IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 (JJF) **PUBLIC VERSION**

DECLARATION OF KAREN JACOBS LOUDEN IN SUPPORT OF WYETH'S ANSWERING MARKMAN BRIEF

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v.	)	C. A. No.: 06-222 (JJF)
IMPAX LABORATORIES, INC., Defendant.	)	**PUBLIC VERSION**

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I, Karen Jacobs Louden, hereby declare as follows:

1. I am a partner with the law firm of Morris, Nichols, Arsht & Tunnell, LLP. I am one of the attorneys representing Wyeth in the current litigation.

2. Attached hereto as Exhibit 22 is a true and correct copy of an excerpt of Gibaldi, *Biopharmaceutics and Clinical Pharmacokinetics* (4th Ed. 1991), pages 124-145.

3. Attached hereto as Exhibit 23 is a true and correct copy of an excerpt of Rowland and Tozer, *Clinical Pharmacokinetics Concepts and Applications* (3rd Ed. 1995), pages 109-136.

4. Attached hereto as Exhibit 24 is a true and correct copy of the Answering Declaration of James W. McGinity, Ph.D., dated May 24, 2007 (with Exhibits A through E).

5. Attached hereto as Exhibit 25 is a true and correct copy of an excerpt of the Manual of Patent Examining Procedure (8th Ed., Rev. Aug. 2006) § 609.02, pages 600-148 through 600-149.

6. Attached hereto as Exhibit 26 is a true and correct copy of an excerpt of the Manual of Patent Examining Procedure (8th Ed., Rev. Aug. 2006) § 707.05, pages 700-115 through 700-116.

7. Attached hereto as Exhibit 27 is a true and correct copy of an excerpt of the Manual of Patent Examining Procedure (7th Ed., July 1998) §§ 609 and 707.05, pages 600-101 through 600-103 and 700-55 through 700-56.

8. Attached hereto as Exhibit 28 is a true and correct copy of an excerpt of the Manual of Patent Examining Procedure (6th Ed., Rev. July 1996) §§ 609 and 707.05, pages 600-89 through 600-91 and 700-52 through 700-53.

9. Attached hereto as Exhibit 29 is a true and correct copy of the Answering Declaration of Ronald J. Sawchuk, Ph.D., dated May 24, 2007 (with Exhibits A through C).

I declare under penalty of perjury that the foregoing is true and correct, and that this declaration was executed on this 25th day of May, 2007.

Karen Jacobs Louden

Karen Jacobs Louden (#2881)

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on June 4, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filings(s) to the following:

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I also certify that copies were caused to be served on June 4, 2007, upon the following in the manner indicated:

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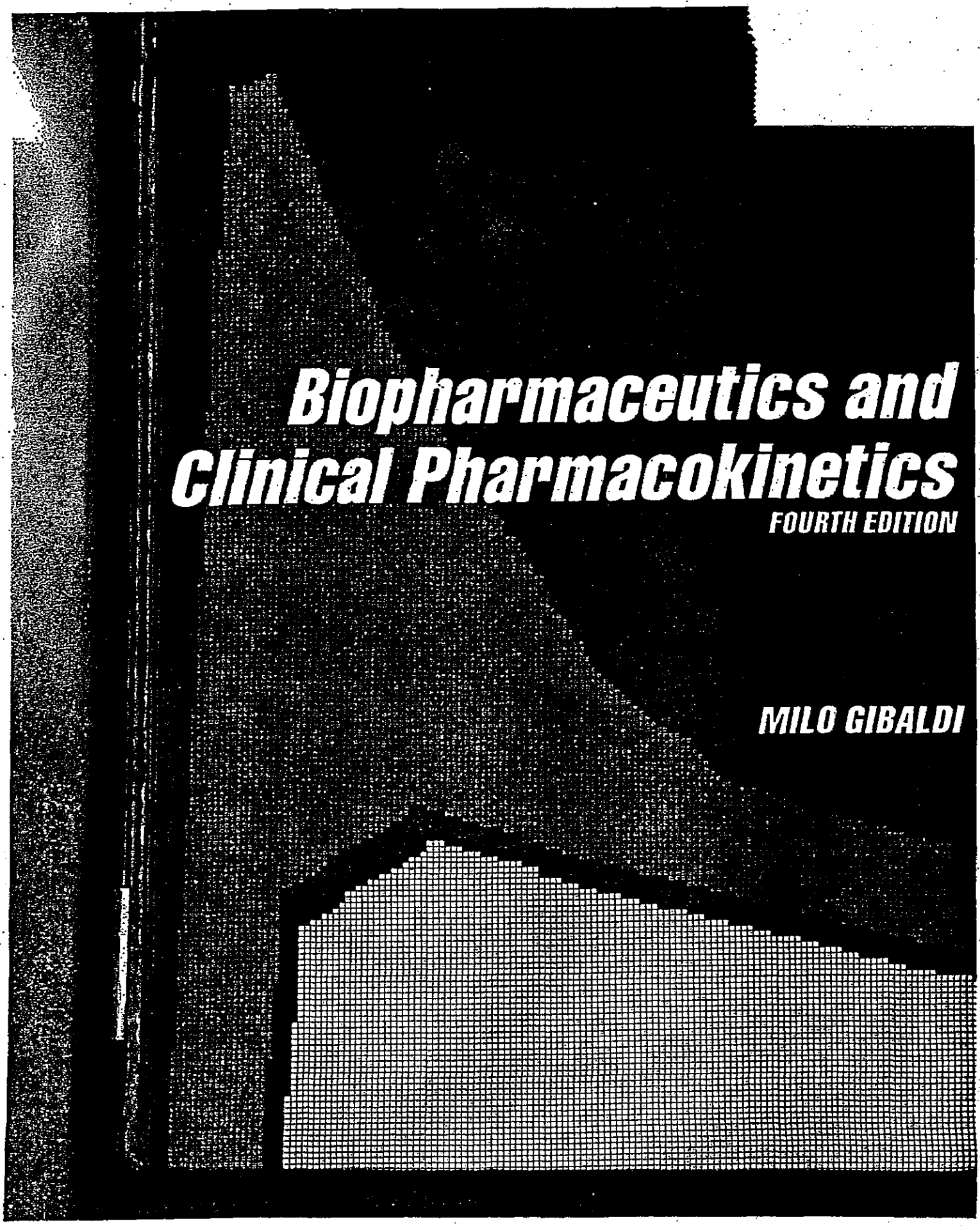
EXHIBIT 22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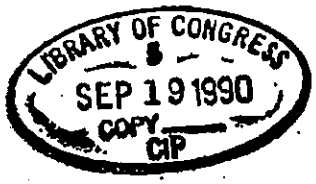

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Prolonged-Release Medication

PHARMACOKINETIC THEORY

The duration of drug effect is a function of the pharmacokinetics of the drug molecule in an individual patient. The clearance and apparent volume of distribution of a drug determine the degree of persistence of the molecule in the body. This persistence is characterized in terms of half-life or mean residence time (MRT). Because the duration of drug action is related to the distribution and elimination kinetics of a drug, the frequency of dosing must also bear some relationship to the drug's half-life or MRT.

We often find that the frequency of dosing needed to maximize the benefit-to-risk ratio of a drug is unreasonable. For example, in most patients, procainamide must be given every 3 to 4 hr around the clock to assure continuous suppression of irregular cardiac rhythms. The same dosing requirements apply to the use of the bronchodilator theophylline in children. The optimum use of idoxuridine eye drops for herpetic keratitis calls for hourly administration.

A particularly conscientious patient may be able to comply with these requirements during the waking hours, but even he is confounded during the sleep period. Excessively frequent dosing requirements do not encourage compliance to the prescribed drug regimen, particularly when the drug is used prophylactically or to treat a silent disease such as hypertension.

The alternative solutions to this important therapeutic problem include giving the drug less frequently and accepting a less favorable therapeutic outcome, seeking new drugs with similar pharmacologic effects but more favorable pharmacokinetic characteristics, or developing a prolonged-release dosage form. In most cases, experience dictates that the pharmaceutical solution be examined first.

Drug Absorption and Duration of Effect

Prolonged-release medication is a dosage form containing more drug than a conventional dosage form but releasing the drug far more slowly, over a period of hours or even days rather than seconds or minutes. In essence, we seek a situation where the duration of drug action is substantially determined by the duration of drug release from the dosage form rather than the drug molecule's pharmacokinetic properties.

This idea can be expressed mathematically by considering the intravenous and oral administration of a drug that distributes rapidly from the bloodstream. After intravenous bolus administration, drug concentration in the blood is given by:

$$C = C_o \exp(-kt) \qquad (7\text{–}1)$$

where C_o is the initial drug concentration and k is the first-order elimination rate constant. Under these conditions, MRT is given by:

$$MRT_{iv} = 1/k \qquad (7\text{–}2)$$

The persistence of drug in the body and the duration of drug effect is a function of drug elimination kinetics.

Following oral administration of the drug, assuming first-order absorption, concentration in the blood is given by:

$$C = C^*F[\exp(-kt) - \exp(-k_a t)] \qquad (7\text{–}3)$$

where C^* is a complex constant, F is the fraction of the oral dose reaching the systemic circulation, and k_a is the first-order absorption rate constant. The MRT is given by the following equation:

$$MRT_{oral} = MRT_{iv} + 1/k_a \qquad (7\text{–}4)$$

The time course of drug concentration in the blood is affected by the absorption process, i.e., $MRT_{oral} > MRT_{iv}$. But, for most drugs, absorption from conventional dosage forms is so rapid that MRT_{oral} is not substantially greater than MRT_{iv}. Accordingly, even after oral administration the duration of effect is largely a function of the elimination kinetics of the drug.

However, if the release rate of drug from the dosage form is decreased (i.e., decrease k_r), we simultaneously increase MRT_{oral}. The MRT becomes more dependent on the release rate and less dependent on the drug molecule's kinetics. Using this approach, a situation is reached where the MRT and the duration of effect are largely controlled by the release rate of drug from the dosage form.

Frequency of Dosing and Therapeutic Index

The *therapeutic index* of a drug is most usefully defined in man as the ratio of the maximum drug concentration in blood that can be tolerated to the minimum drug concentration needed to produce a satisfactory clinical response. Therapeutic concentration ranges for certain drugs in man have been identified. In some cases, these ranges are narrow, resulting in small therapeutic indices.

The average therapeutic range of theophylline concentration in blood is about 8 to 20 μg/ml; the therapeutic index of theophylline is 2.5. Estimates of therapeutic index for other drugs are 2.0 for digoxin and valproic acid, 2.7 for procainamide, and 4.0 for lidocaine. We seek to maintain drug concentrations in blood well within the therapeutic range during drug therapy. This requires not only the selection of an appropriate daily dose; the drug must also be given with sufficient frequency so as to minimize the range of blood concentrations that are produced. The ratio of maximum to minimum drug concentrations at steady state should not exceed the therapeutic index of the drug. This concentration ratio is a function of the half-life of a drug and the frequency of dosing.

For drugs that are both absorbed and distributed rapidly, Theeuwes and Bayne[1] have demonstrated the following relationship:

$$\tau < t_{1/2} (\ln TI)/(\ln 2) \qquad (7\text{–}5)$$

where τ is the dosing interval, $t_{1/2}$ is the half-life, and TI is the therapeutic index. A drug with a therapeutic index of 2 and a half-life of 3 hr must be given no less frequently than every 3 hr to avoid excessive or subtherapeutic concentrations. A drug with a similar half-life but a therapeutic index of 4 may be given every 6 hr.

When drug effects are directly related to concentration in blood but distribution is slow, the drug must be given even more frequently than suggested by Equation 7–5. In such cases, a better estimate of dosing interval may be obtained by replacing $t_{1/2}$ with 0.693(MRT) where MRT is the mean residence time.

Steady-State Concentrations and Release Rate

Dosing regimens for rapidly absorbed drugs are a function of the pharmacodynamic and pharmacokinetic characteristics of the drug molecule; they must be based on the therapeutic index and half-life or MRT of the drug itself. Reducing the absorption rate of a drug by controlling its release rate from the dosage form, however, can dramatically affect drug concentrations at steady state. For a given dosage regimen, the slower the release rate of drug, the smaller is the ratio of maximum to minimum drug concentrations at steady state. Under these conditions, we can give larger doses at less frequent intervals and still stay within the therapeutic concentration range of the drug; this is the rationale for prolonged-release medication.

Prolonged-release medication offers obvious advantages for drugs with short half-lives and small therapeutic indices. These specialized dosage forms permit such drugs to be given at more reasonable intervals throughout the day; implications include more optimal therapy, patient convenience, and improved patient compliance with the prescribed regimen. The application of prolonged-release medication, however, is not limited to such drugs. Since these dosage forms offer the potential of reducing the peak-to-trough drug concentration ratio, they may be useful for many more drugs.[2]

Reducing the peak-to-trough concentration ratio has been found to improve the benefit-to-risk ratio of some drugs. The potassium-depleting effect of hydrochlorothiazide disappears, while its diuretic effect is slightly enhanced, when the drug is given every 3 hr rather than once a day.[3] The nephrotoxicity of gentamicin is substantially reduced when steady-state concentrations are maintained in a narrow range of about 1 to 4 μg/ml.[4] The safety of certain anticancer drugs, including bleomycin[5] and methotrexate,[6] is increased when given continuously by infusion rather than intermittently.

By minimizing fluctuations in blood levels we may be able to reduce the dosage required, improve the effectiveness, and decrease the adverse effects of a drug. For instance, pilocarpine administered continuously by an ocular insert reduces elevated intraocular pressure in patients with glaucoma without the marked myopia commonly seen in patients using pilocarpine eyedrops every six hours.

White[7] compared intraoperative and postoperative effects of fentanyl and ketamine administered by continuous intravenous infusion with those produced by intermittent iv bolus doses. Continuous infusion minimized the peaks and valleys of drug concentration in blood and, presumably, brain that ordinarily result from intermittent dosage.

Women scheduled for elective outpatient gynecologic surgery received either fentanyl or ketamine as an intravenous adjunct to nitrous oxide for maintenance of general anesthesia after induction with thiopental. The drugs were given either by continuous iv infusion or intermittent iv bolus. The method of drug administration resulted in important differences.

Only about one-half the dosage of fentanyl or ketamine was needed to maintain anesthesia when the drugs were given by continuous infusion rather than by intermittent bolus. The use of less drug resulted in more rapid recovery from anesthesia and in substantially less postoperative sedation, and minimized postoperative psychomotor dysfunction. Excessive sedation was noted in about 50% of the patients in the bolus groups but in less than 10% of the patients in the infusion groups.

Continuous infusion also improved intraoperative conditions. Respiratory depression and muscular rigidity occurred less frequently with continuous rather than intermittent administration of fentanyl. Hypertension and tachycardia occurred less frequently with continuous rather than intermittent ketamine.

Zero-Order Release

Continuous, constant-rate intravenous infusion leads to constant blood levels. Under these conditions, blood levels are invariant with time; there are no peaks or troughs. Provided that the constant drug concentration is within the therapeutic range, this is an ideal situation for many drugs. The only way to achieve constant blood levels is to administer the drug at a constant (zero-order) rate over the entire dosing interval. The concentration of drug at steady state is given by the following equation:

$$C_{ss} = k_0/Cl \qquad (7\text{–}6)$$

where k_0 is the zero-order delivery or release rate of drug, and Cl is the clearance of the drug. Fluctuations in blood levels do occur under these conditions, because of temporal variations in clearance or in the delivery rate, but they are usually small.

Until recently, constant rate intravenous infusion, by means of a carefully controlled drip or mechanical pump, was the only way to attain constant blood or tissue levels of drug. Today, there are dosage forms intended for oral, ocular, intravaginal, or intramuscular administration that release drug in a zero-order or near zero-order fashion. These dosage forms are discussed in other sections of this chapter.

ORAL MEDICATION

Most prolonged-release dosage forms are intended for oral administration. A prolonged-release dosage unit contains more drug than a conventional dosage unit but is intended to be given less frequently. A drug that is ordinarily given at a dose of 250 mg 4 times a day in a conventional tablet or capsule may be given at a dose of 500 mg twice a day, or 1 g once a day, in a prolonged-release dosage form. The ultimate criteria for evaluating such dosage forms are: (1) the amount of drug intended to be absorbed is indeed absorbed in a predictable and consistent manner; and (2) the steady-state ratio of maximum to minimum drug concentrations is no greater than or, optimally, less than that produced by the more frequently administered conventional dosage form.

The early history of the prolonged-release oral dosage form is probably best forgotten. Products were developed empirically, often with little rationale, and bioavailability problems were common. Many people viewed these dosage forms as little more than marketing inducements. Today, the situation has improved; many of the available products are well designed drug delivery systems and have a defined therapeutic goal. In some cases, the prolonged-release dosage form is the most important and most frequently used form of the drug.

A wide variety of techniques have been used to develop prolonged-release oral dosage forms. These techniques include the use of drug substances of decreased solubility or dissolution rate, accomplished by increasing particle size or substi-

tuting less soluble salts or complexes, ion exchange resins to bind the drug substance, porous, nondisintegrating, inert carriers as matrices for the drug, slowly eroding coatings or matrices, and coatings that serve as membranes for drug diffusion.

Most oral prolonged-release dosage forms can be characterized as either subdivided or single units. Subdivided prolonged-release dosage forms, exemplified by the hard gelatin capsule containing numerous drug-impregnated beads, present the drug to the gastrointestinal tract in the form of many slowly-dissolving particles or granules. Often, several kinds of beads are found in the capsule, some releasing the drug rapidly, others releasing the drug over a period of several hours, still others releasing the drug at intermediate rates. Spansule is a trade name historically associated with this dosage form. More details of these and other formulations can be found in a recent review by Longer and Robinson.[8] Phenothiazines, antihistamines, iron, and many other drugs are available in this kind of dosage form. In general, the release and absorption of drugs from slow-release beads can be described by first-order kinetics.

The single-unit prolonged-release dosage form remains more or less intact throughout the gastrointestinal tract, releasing the drug continuously during its passage down the tract. An example of this dosage form is the inert plastic matrix, a dosage form that has been used widely in Europe. The drug is mixed with inert, insoluble, powdered matrix material consisting of plastic resins and other ingredients and compressed. In the gastrointestinal tract, drug particles from the surface of the matrix system dissolve and leave pores through which drug from within the tablet leaches out. The matrix retains its shape during the leaching process and is eliminated in the feces. The release rate of drug decreases with time and, in this sense, resembles a first-order process.[9]

The steady-state plasma levels and pharmacologic effects of a daily dose of 0.2-g metoprolol, a cardioselective β-blocker, in a prolonged-release matrix tablet and in regular 0.1-g tablets were studied in healthy subjects. The following dosing regimens were used: (1) one prolonged-release tablet once a day; (2) two 0.1-g regular tablets once a day; and (3) one 0.1-g regular tablet every 12 hr. The peak-to-trough concentration ratio of metoprolol was, on the average, about 10 for the matrix tablet and the twice-a-day regimen and about 40 for the once-a-day administration of the regular tablets (Fig. 7–1). Metoprolol in the matrix tablet produced a more uniform effect on heart rate and systolic blood pressure during exercise than the corresponding daily dose of metoprolol given as two 0.1-g tablets once daily or as one 0.1-g tablet twice a day.[10] Although metoprolol has a relatively short half-life, about 3 hr, a once-a-day regimen can be developed with a prolonged-release dosage form. The same is true for propranolol.[11]

Some pharmaceutical scientists judge subdivided prolonged-release dosage forms to be potentially safer than intact or single-unit dosage forms because a mechanical failure of the coating or matrix would result in the immediate release of only a small fraction of the entire dose. Mechanical failure is unlikely to occur with the matrix tablet, but it may occur in those single-unit dosage forms that rely on a continuous membrane to control release. A failure in this case may result in the immediate dumping of the entire dose, a quantity of drug that is 2 or 3 times the amount given as a single dose in a conventional dosage form.

Because prolonged-release products are complex dosage forms, substantial differences in performance among different products of the same drug may occur. Although the prolonged-release matrix tablet of metoprolol, previously described, has a longer duration of effect than the same dose of the drug given as regular tablets,[12] this is not true for a different prolonged-release product of metoprolol.[13,14] One product shows a significant improvement over conventional metoprolol whereas the other does not.

Considerable differences among prolonged-release products of theophylline have also been reported. Studies in adult subjects indicate that theophylline is slowly but completely and consistently absorbed from three of six prolonged-release formulations. Theophylline absorption from the other three products is more erratic and less complete.[15] In another study, theophylline absorption from three commercial products labeled as prolonged-release was compared to the absorption from a standard uncoated tablet. Two of the prolonged-release products showed considerably slower absorption of theophylline than did the regular tablet, but the third product did not.[16]

To determine whether clinically important changes in serum theophylline concentrations occur when patients switch their brand of prolonged-release theophylline, 10 subjects with asthma were given the same dose of four different

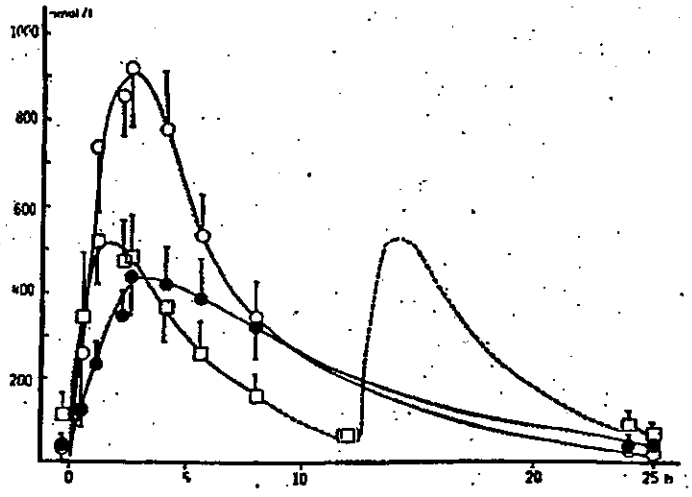

Fig. 7–1. Mean steady-state plasma concentrations of metoprolol after repetitive dosing of a prolonged-release tablet (0.2 g) once a day (●), two 0.1 g regular tablets once a day (○), and one 0.1 g regular tablet every 12 hr (□). (From Johnsson, G., et al.[16])

commercially available products for 2-week periods in a random, double-blinded, crossover fashion.[17]

On at least one occasion in every subject, switching between brands of theophylline resulted in serum theophylline levels outside the accepted therapeutic range, and this was associated with toxic symptoms in 5 of the subjects. Worsening pulmonary function was observed in two subjects when switching resulted in lowered theophylline levels. Many of the changes in theophylline concentrations on switching from one brand to another could not be predicted by the bioavailability differences between the products. The investigators concluded that "these results argue against the open substitution of these formulations and suggest that if patients are switched between different brands of SR theophylline, their serum theophylline concentration needs to be closely monitored."

Much has been published concerning prolonged-release theophylline during the past 10 years. The drug has a relatively short half-life, particularly in children, and a small therapeutic index. Clinical studies suggest that 40% of all children receiving conventional products of theophylline in the usual every 6-hr manner will have excessive or subtherapeutic blood levels of the drug.[18]

Although no well-controlled clinical trials have been published showing that prolonged-release theophylline preparations are more effective than plain theophylline tablets or solutions, many clinicians report that the long-acting formulations are more effective in controlling symptoms, especially during the night. Furthermore, compliance is likely to improve when patients take medication only twice a day, rather than 3 or 4 times a day. On the other hand, some clinicians have found that when adverse effects occur with prolonged-release theophylline, they persist longer. Some patients taking the long-acting preparations complain of insomnia, a known adverse effect of theophylline.

Adult smokers and children, who metabolize theophylline rapidly, may benefit most from treatment with prolonged-release preparations. In many patients, it may be necessary to individualize the daily dose and, in some patients, it may be necessary to give the product more frequently than twice a day.

Individual variability in dosing requirements is clearly seen in the results of a study evaluating one of the more commonly prescribed prolonged-release theophylline preparations, Theodur.[19] In a panel of 20 asthmatic patients, 6 to 18 years of age, receiving the long-acting theophylline product twice a day, the daily doses needed to produce an average blood level of about 15 μg/ml ranged from 6.1 to 16.3 mg/kg. The blood levels resulting from these individualized regimens, as estimated from 4 to 5 blood samples taken over the course of each of 2 consecutive steady-state dosing intervals, showed surprisingly little fluctuation. Peak and trough values and peak-to-trough ratios for the 20

Table 7–1. Peak and Trough Serum Concentrations of Theophylline During 24 hr at Steady State in Children Receiving, on the Average, 10 mg/kg Twice a Day in a Prolonged-Release Product.*

Patient	Peak concn. (μg/ml)	Trough concn. (μg/ml)	Peak-to-trough ratio
1	17.6	10.3	1.7
2	22.7	12.7	1.8
3	17.0	12.0	1.4
4	22.9	14.8	1.5
5	16.4	11.2	1.5
6	18.9	12.4	1.5
7	17.2	7.0	2.5
8	21.8	16.3	1.3
9	13.7	8.7	1.6
10	15.5	12.6	1.2
11	20.3	16.6	1.2
12	18.5	9.0	2.1
13	18.4	10.6	1.7
14	19.7	12.1	1.6
15	17.6	10.5	1.7
16	20.3	15.4	1.3
17	17.5	11.8	1.5
18	23.5	16.7	1.4
19	14.5	7.6	1.9
20	16.8	10.4	1.6

*Data from Kelly, H.W., and Murphy, S.[19]

patients are shown in Table 7–1. Average blood levels are shown in Figure 7–2. If twice-a-day doses of regular theophylline, sufficient to produce average levels of about 15 μg/ml, were given to these patients we would expect to find peak-to-trough concentration ratios of about 10.

A circadian variation in theophylline levels in serum is quite evident during treatment with certain twice-a-day slow-release theophylline products. Steady-state theophylline concentrations for the 12-hr period following the morning dose are different from those following the evening or night dose. In one study, peak concentration at steady state after an 11 AM dose occurred at about 3 hr after dosing, whereas peak level was observed at about 9 hr following the 11 PM dose, which was taken immediately before retiring.[20] The area under the concentration-time curve during a dosing interval at steady state was also smaller after the night dose than following the morning dose. These differences reflect a circadian variation in theophylline absorption rather than in theophylline metabolism.

A change in posture could be a simple explanation of the circadian variation in theophylline pharmacokinetics.[21] This was examined in healthy human subjects who took 450 mg slow-release aminophylline orally at the same time of day on two separate occasions. On one day the subjects remained standing and on the other, they lay supine throughout the study. Theophylline levels in plasma were measured hourly for 6 hr after the dose.

At each sampling time, theophylline levels were higher during the standing experiment than during the supine study. Peak concentration of theophylline with the subjects standing occurred at 5 hr and was 6.4 mg/L. Theophylline levels were ascending for the entire 6-hr study period in the supine group;

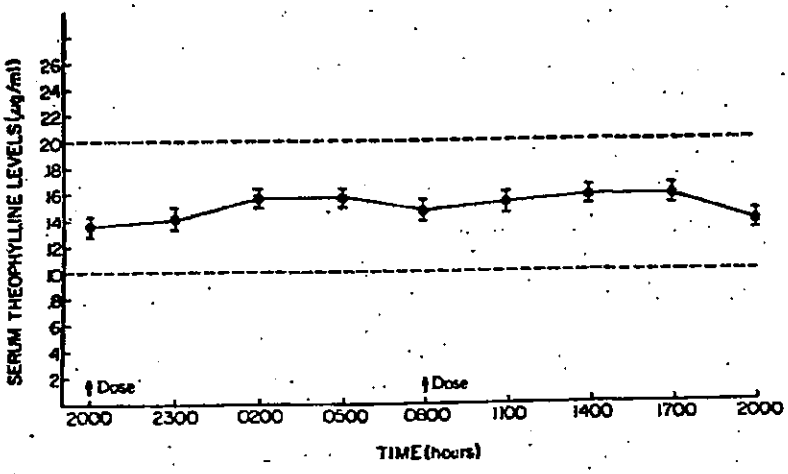

Fig. 7–2. Mean steady-state serum concentrations of theophylline in children receiving an average dosage of 10 mg/kg in a prolonged-release product every 12 hr. (From Kelly, H.W., and Murphy, S.: Efficacy of a 12-hour sustained-release preparation in maintaining therapeutic serum theophylline levels in asthmatic children. Pediatrics, 66:100, 1980. Copyright American Academy of Pediatrics 1980.)

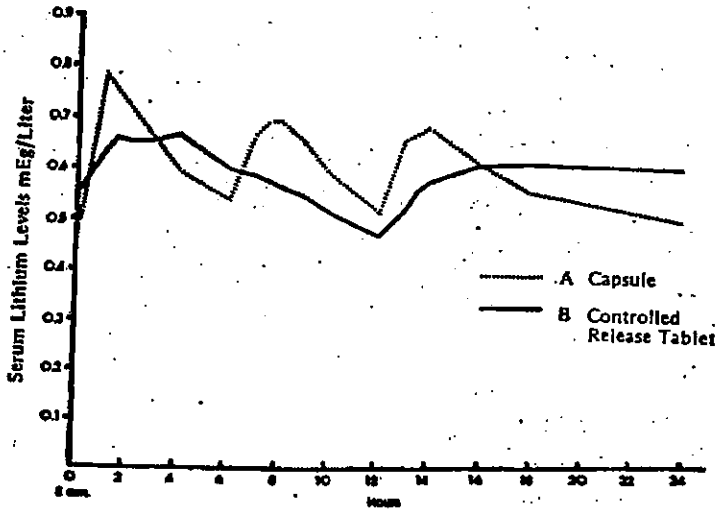

Fig. 7–3. Mean steady-state serum levels of lithium in healthy subjects who received a 300-mg capsule 3 times a day or a 450-mg prolonged-release tablet twice a day. (From Caldwell, H.C., et al.[24])

mean concentration at 6 hr was 5.4 mg/L. The investigators concluded that the supine position assumed at bedtime may be an adequate explanation for the diurnal variation seen with twice-a-day prolonged-release theophylline products.

Theophylline is widely used in children, so it is not surprising that slow-release tablets are sometimes chewed or crushed to facilitate swallowing. This practice may result in a loss of the prolonged-release characteristic of the product. To examine this question, Theo-Dur, a widely used formulation, was given to healthy adult subjects on three occasions, at least 1 week apart.[22] On the first day, subjects were randomly allocated to either swallow intact or chew, and then swallow, a 300 mg tablet. Subjects were then crossed over for the second dose. The effects of crushing the tablet prior to ingestion were studied at the third dose. Swallowing the tablets intact resulted in a significantly longer time to peak concentration compared with chewing or crushing (i.e., 6 hr *vs* about 3 hr) and the peak concentration was somewhat lower, 35.6 μmol/L, compared with chewing (43.1 μmol/L) or crushing (41.9 μmol/L). Area under the curve, however, was about the same for all three modes of administration. Chewing or crushing Theo-Dur tablets does not appear to have a substantial effect on the bioavailability characteristics of the product, suggesting that it may be a suitable preparation for use in young children.

A prolonged-release liquid theophylline preparation, aimed at the pediatric population and designed for twice-daily administration, is under investigation.[23] The suspension was compared with aminophylline solution (administered every 8 hr) in 27 asthmatic children less than 12 years of age. Average steady-state levels of theophylline were about 10% lower during treatment with the suspension than with the solution. Peak levels were also lower (11.2 vs 14.2 μg/ml) and the difference between C_{max} and C_{min} was smaller (6.9 vs 10.0 μg/ml) with the suspension. The investigators concluded that the slow-release suspension should prove to be useful in patients who require maintenance theophylline therapy, but who cannot take solid oral dosage forms.

Lithium carbonate is the drug of choice in treating certain phases of manic depression. Although the drug has a long half-life, about 24 hr, it also has a narrow therapeutic index and must be given 3 or 4 times a day. Steady-state serum level fluctuations of lithium were compared following regular capsules (300 mg 3 times a day) or prolonged-release tablets (450 mg every 12 hr) of lithium carbonate.[24] Average blood levels are shown in Figure 7–3. The degree of fluctuation (Fl) of serum levels was assessed by the following equation:

$$Fl = (C_{max} - C_{min})/\overline{C} \qquad (7\text{–}7)$$

where C_{max} and C_{min} are the maximum and minimum drug concentrations over the 24-hr steady-state dosing cycle, and $\overline{C}$ is the mean concentration

over the cycle. $\overline{C}$ is estimated from the ratio of area under the curve to dosing interval. This fluctuation index is analogous to the coefficient of variation; small values are desired for the prolonged-release preparation. This index may be more stable than the peak-to-trough concentration ratio, which could be highly unstable in the presence of error for small values of C_{min}. In this study, the index was 0.46 for the prolonged-release tablet regimen and 0.66 for the regular capsule regimen, suggesting that the regular product produces about 40% more fluctuation in serum lithium levels than the slow-release formulation.

Fluctuations in serum levels are related not only to the release rate of drug from the dosage form and the frequency of administration (dosage interval), but also vary with drug elimination rate. Steady-state studies with a prolonged-release theophylline product found a linear relationship between percent fluctuation and theophylline clearance in individual subjects.[25]

Weinberger and Hendeles[26] also calculated the percent fluctuation in steady-state serum levels of theophylline for different products. With one prolonged-release product, percent fluctuation was 57% in slow metabolizers of theophylline (half-life = 7.7 hr) but increased to 154% in rapid metabolizers (half-life = 3.7 hr).

Several antiarrhythmic drugs are plagued with the undesirable characteristics of short half-life and narrow therapeutic index. Procainamide is an example; its half-life is about 3 hr. Therapeutic and toxic effects have been related to drug concentrations in plasma. The therapeutic range is 4 to 8 μg/ml but can often extend to 10 μg/ml without toxicity. To maintain safe, adequate blood levels, the regular tablet form of the drug must be given every 3 to 4 hr.

Steady-state levels of procainamide were determined in patients receiving about 20 mg/kg per day in the form of prolonged-release matrix tablets of the drug every 8 hr.[27] Mean procainamide blood levels are plotted in Figure 7–4. In 17 of the 26 patients, blood levels were maintained above a level of 4 μg/ml for at least 75% of the time. Of the 9 patients showing blood levels below the minimum level for more than 25% of the time, 8 would have benefited from an increased daily dose or improved compliance with the regimen. In 4 of the 26 patients, blood levels were above 10 μg/ml for more than 10% of the time. All 4 patients required a lower daily dose and, possibly, more frequent administration. The results suggest that this prolonged-release form of procainamide, given every 8 hr, would benefit most patients if the daily dose were individualized.

Disopyramide is another orally effective antiarrhythmic; its electrophysiologic properties are similar to those of quinidine and procainamide. A therapeutic range of 2 to 4 μg/ml has been suggested for the drug. Because of its short half-life, disopyramide must be given 4 times a day to maintain safe and effective concentrations in plasma. Disopyramide concentrations were determined in plasma following repeated doses of regular capsules (150 mg every 6 hr) or prolonged-release matrix tablets (300 mg every 12 hr) to patients with various kinds of arrhythmia.[28] A level of 4 μg/ml with regular capsules was exceeded by 2 patients, and 1 patient exceeded this level with the matrix tablet. None of the patients had a level below 2 μg/ml. The average steady-state peak-to-trough concentration ratio was 1.4 for the capsules and 1.6 for the prolonged-release tablets. The average fluctuation index was 0.36 for the regular product and 0.43 for the prolonged-release preparation. Although the matrix tablet was given only half as frequently as the regular capsules, little difference in blood levels of disopyramide was noted between products. The matrix tablet of disopyramide appears to be a useful prolonged-release form of the drug.

Drugs absorbed by specialized, capacity-limited transport processes are ordinarily not good candidates for prolonged-release dosage forms. Facilitated absorption is often site-specific and drug released beyond this site in the intestine is usually poorly absorbed. Iron may be an exception. A prolonged-release preparation containing 100 mg of ferrous iron, given twice daily, was compared to a conventional tablet containing 50 mg of ferrous sulfate, given 4 times daily. In patients with iron deficiency anemia, more iron was absorbed from the slow-release preparation.[29]

Prolonged-release forms of drugs such as nitrofurantoin[30] or lithium[31] have been investigated for reducing the incidence of nausea and vomiting resulting from gastrointestinal irritation or high blood concentration peaks. Studies with lithium in human subjects show that rapidly disintegrating tablets generally produce more nausea than do prolonged-release tablets. The incidence of this side effect appears to correlate with high concentrations of lithium in the stomach and proximal intestine.

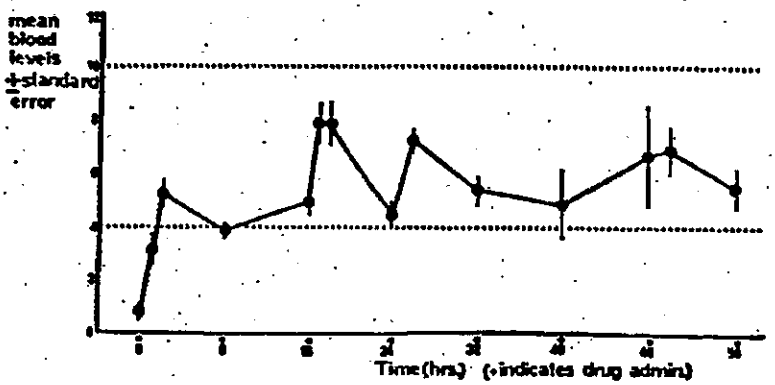

Fig. 7–4. Mean levels of procainamide during repetitive dosing of a prolonged-release tablet every 8 hr. (From Cunningham, T., Sloman, G., and Nyberg, G.[27])

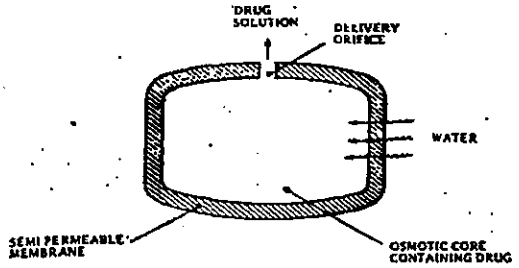

Fig. 7–5. Cross section of an elementary osmotic pump (EOP) designed to release drug in a zero-order (constant-rate) manner. (From Theeuwes, F.[33] Reproduced with permission of the copyright owner.)

On the other hand, the slower the release of lithium from a dosage form, the higher is the incidence of diarrhea. This adverse effect seems to be related to high concentrations of lithium in the distal intestine, a situation found only with prolonged-release products.[31] More recent studies confirm these results.[32]

Zero-Order Release

The ideal approach to minimizing blood level fluctuations of a drug is to have zero-order release from the dosage form. A system, termed the elementary osmotic pump (EOP), is now available to achieve this goal. Figure 7–5 shows a diagram of this dosage form, which resembles a coated tablet. The EOP tablet contains a solid core of drug and adjuvants coated with a polymer membrane, permeable to water and interrupted only by a single small orifice with a diameter of 0.1 to 0.4 mm.[33] After the tablet is swallowed, the membrane selectively admits water from the gastrointestinal tract; drug within the membrane is gradually dissolved. The internal pressure produced by entry of the water forces the drug solution out of the orifice. Since the volume of the system is fixed, constant-rate release is achieved. Typically, 60 to 80% of drug content is delivered at a constant rate; the rest of the dose is released in a pseudo-first-order fashion. The depleted membrane sac is excreted intact. Release rates as high as 60 mg/hr may be achieved with this dosage form. Drug release is independent of pH or motility.

The duration of drug delivery is controlled by the permeability of the membrane and the composition of the core. At a given rate of drug delivery, the duration of controlled release is determined by the amount of drug in the core. In practice, however, the duration of release is limited by intestinal transit time and probably cannot exceed 8 to 12 hr without compromising the extent of absorption.

The hemodynamic effects and plasma levels of metoprolol have been determined after single and multiple doses of EOP tablets or more conventional prolonged-release tablets of the drug.[27] Both dosage forms were given once a day for 8 days to healthy subjects. The prolonged-release tablets contained 200 mg metoprolol tartrate; the EOP tablets contained 190-mg metoprolol fumarate (equivalent to 200 mg of the tartrate) with a 19 mg/hr zero-order release rate. Both formulations reduced exercise heart rate and exercise systolic blood pressure for the entire 24-hr steady-state dosing interval, but the EOP tablets elicited a more uniform response. Mean steady-state plasma profiles of me-

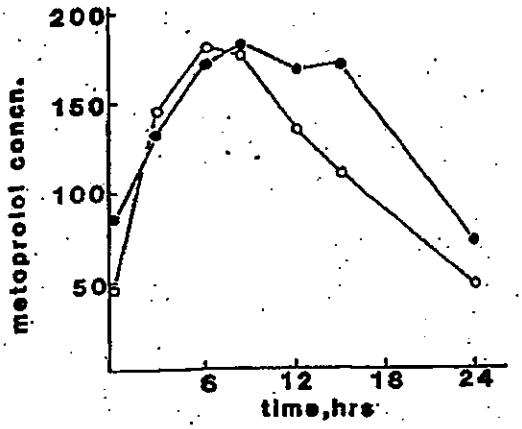

Fig. 7–6. Mean steady-state plasma concentrations of metoprolol (ng/ml) in healthy subjects after repetitive dosing of an EOP prolonged-release product (●) or a more conventional prolonged-release product (○), once a day. (Data from Kendall, M.J., et al.[34])

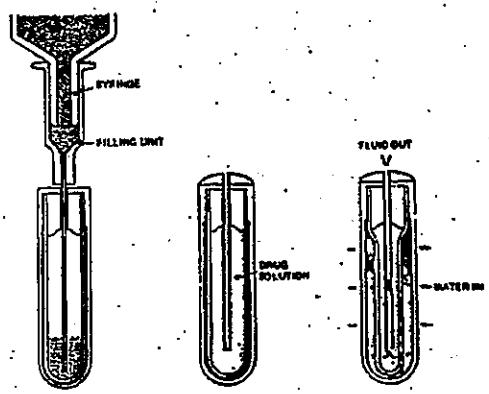

Fig. 7–7. Schematic representation of the filling and operation of the osmotic pump. (From Eckenhoff, B., and Yum, S.I.[38] By permission of the publishers, Butterworth & Co. Ltd. Copyright 1981.)

toprolol are shown in Figure 7–6. Peak-to-trough concentration ratios were 4.5 for the conventional prolonged-release tablets and 2.6 for the EOP tablets. Fluctuation indices were 1.31 for the prolonged-release tablets and 0.88 for the EOP tablets. Both hemodynamic and pharmacokinetic criteria support the superiority of the EOP tablet.

The steady-state metoprolol levels produced by the EOP tablets show considerable fluctuation over the dosing interval even though release rate approximated zero-order. This occurs because release took place over a relatively small fraction (10 out of 24 hr) of the dosing interval. To obtain constant blood levels, there must be constant-rate release over the entire dosing interval. This situation was more closely approximated in studies with acetazolamide, a drug that reduces intraocular pressure, in EOP tablets.[35] Relatively constant blood levels of acetazolamide were obtained by dosing every 12 hr with EOP tablets that release the drug over an 8-hr period, or about three quarters of the dosing interval.

Bayne et al.[36] described the evaluation of constant release rate dosage forms of indomethacin, based on the elementary osmotic pump principle and intended to be taken twice a day. Indomethacin is usually given 3 or 4 times a day in the treatment of rheumatoid arthritis and osteoarthritis.

Steady-state levels of indomethacin were determined in plasma of healthy subjects who had received 150 mg/day for 5 days according to the following regimens: (a) controlled-release tablet delivering drug over 8 hr, given twice a day; (b) controlled-release tablet delivering drug over 11 hr, given twice a day; (c) regular capsules of indomethacin given 4 times a day; (d) regular capsules given 3 times a day.

Average indomethacin levels in plasma at steady state were similar for all four regimens, but subjects taking the prolonged-release dosage forms showed much less fluctuation in plasma levels of drug than subjects taking regular capsules. Also, trough levels of indomethacin before the morning dose were significantly higher during treatment with controlled-release tablets than with regular capsules. This difference may be important for the relief of morning stiffness often seen in arthritics.

Generic osmotic pumps are also available as experimental tools for animal or clinical studies. They are useful for, but not limited to, oral administration.[9,37,38] A diagram of this dosage form is shown in Figure 7–7. The reservoir is filled with a drug solution. The wall of the reservoir is inert, impermeable, and flexible. A sleeve of osmotically active agent is placed between the reservoir wall and the rigid semipermeable membrane.

Water from the surroundings is imbibed through the outer membrane into the osmotic sleeve at a rate controlled by the permeability of the membrane and the osmotic pressure difference across the membrane. The incoming water squeezes the reservoir and drug solution is expelled in a constant-volume per-unit-time fashion. Delivery of

drug solution continues at a constant rate until the drug reservoir is completely collapsed.

Limitations of Prolonged-Release Medication

A factor that circumscribes the use of oral prolonged-release medication is the limited residence time of the dosage form in the small intestine. Absorption from the colon may be poor or unpredictable. Hence, small intestine transit time is often of paramount importance in determining the bioavailability of the drug from this dosage form.

The gastrointestinal transit of a radiolabeled osmotic tablet (elementary osmotic pump) has been monitored in groups of young and elderly healthy human subjects.[39] Gastric emptying and small intestine transit were similar for both groups of subjects. Gastric emptying of the tablet when given after a light breakfast (orange juice, cornflakes, and milk) averaged about 3 hr; the tablets arrived at the cecum, on average, about 7 hr after dosing.

In another study, the position in the gastrointestinal tract of an orally administered osmotic tablet containing a radiolabel and oxprenolol, a beta-blocker available in Europe, was followed in fasted subjects by gamma scintigraphy.[40] Gastric emptying times (about 1 hr) and the time to arrival in the colon (about 4 hr) were relatively consistent from one subject to another.

On the other hand, there were wide individual variations in colonic transit with values ranging from 2.5 to 27.5 hr. Accordingly, total transit time ranged from 6 to 32 hr. In the individual with the most rapid colonic transit and total transit, the bioavailability of oxprenolol was only 14%, and 79% of the administered dose was recovered in the stool. In the two individuals with the slowest colonic transit, bioavailability was 40% and 54%.

External gamma scintigraphy was also used to monitor the gastrointestinal transit of radiolabeled prolonged-release tablets containing 800 mg ibuprofen in fasted healthy subjects.[41] The tablet was formulated using an erodible polymer matrix system.

The gastric retention time of the tablets ranged from 10 to 60 min, with a mean value of 35 min. Transit time of a tablet through the small intestine was calculated by subtracting gastric residence time from the time at which the tablet was observed to enter the large bowel. Small bowel transit time ranged from about 2 to 8 hr, with a mean value of 4.7 hr. Again, total transit time was variable (8 to 18 hr) and largely dependent on large bowel residence time, which ranged from 6 to 14 hr.

A statistically significant correlation ($r = 0.89$) was observed between the area under the curve for 24 hr after administration of ibuprofen and total gastrointestinal transit time. Area under the curve for the subject with the most rapid total transit time (8 hr) was only 94 μg-hr/ml compared with a mean value for the group of 180 μg-hr/ml.

For dosage forms like the matrix tablet or the elementary osmotic pump, which remain intact in the gastrointestinal tract, we usually assume an average effective absorption time of 9 to 12 hr after administration. The release rate of drug from the dosage form must be programmed accordingly. Slower release rates run the risk of poor bioavailability. For dosage forms with similar transit times that release drugs in an apparent first-order manner, release half-lives should not exceed 3 to 4 hr.

Since there is a limit to how much we can reduce the release rate of a drug from certain prolonged-release dosage forms without compromising bioavailability, there is also a limit as to how much we can prolong the duration of drug action by these oral dosage forms. Mathematical simulations of the time course of drug in the blood on multiple dosing of slow-release dosage forms suggest that ordinarily drugs with relatively short half-lives (i.e., less than or equal to 6 hr), and low therapeutic indices (i.e., less than or equal to 3) should be given no less frequently than every 12 hr.[3]

Prolonged-release dosage forms that consist of beads, pellets, or particulates, or that disintegrate into particulates, may be retained in the small intestine for longer periods. The small intestine transit time of pellets depends on size, density, and composition. One study found that increasing the density of standardized pellets from 1.0 to 1.6 increased the average transit time from 7 to 25 hr,[42] but these results could not be confirmed.[43]

We still cannot predict the effect of food on the bioavailability of drugs given in prolonged-release dosage forms. Investigators recently studied the effect of food-related changes in gastric emptying on the absorption of procainamide from a nondisintegrating wax-matrix sustained-release tablet. Gastric residence time was greater in fed than in fasted subjects (3.5 vs 1 hr), but food had no effect on the time required to detect procainamide in plasma, on the time to reach peak concentration of procainamide, or on the extent of absorption of procainamide.[44] A standard meal also had little ef-

fect on the absorption of pseudoephedrine from a slow-release capsule formulation based on a system using both ion exchange technology and a wax coating.[45]

The effect of food on drug absorption kinetics may differ markedly from one prolonged-release formulation to another. Theophylline is a case in point. Food has little effect on the absorption profile for theophylline after administration of Theo-Dur, a well-absorbed and widely prescribed slow-release theophylline product.[46] The pediatric version of this product, Theo-Dur Sprinkle, is also completely absorbed in fasting subjects but less than half the dose is absorbed when it is taken after breakfast.[47]

Scandinavian scientists reported the results of a study with children and adults who were given a single dose of a prolonged-release theophylline preparation (Theolair-SR) after an overnight fast and later after a standardized breakfast.[48] Food dramatically reduced the absorption rate of theophylline (see Fig. 7–8), particularly in the children, but it had no effect of the extent of absorption.

About two-thirds of the dose of theophylline is absorbed after administration of Uniphyl, another slow-release product, to fasted subjects, whereas 85% of the dose is absorbed when it is given after a meal.[49] Although there is an increase in bioavailability with food, there is little effect on the rate of absorption of theophylline. Theo-24, a once-a-day theophylline product, is also incompletely absorbed in fasting subjects. With this product, however, food not only increases the extent of absorption, but also greatly increases the rate of absorption with about half the daily dose absorbed in a 4-hr period, giving rise to excessively high blood levels of theophylline.[50]

Exposure of the distal small intestine and colon to drug is far more likely when a prolonged-release formulation rather than a conventional tablet or capsule is taken. In some cases, this may result in a higher incidence of lower bowel toxicity. Microorganisms in the lower bowel may enzymatically reduce a drug, leading to metabolites that are not ordinarily seen after administration of the drug in conventional dosage forms. Bacterial metabolism may decrease bioavailability or result in toxic metabolites.

Drugs that are metabolized and inactivated by the gastrointestinal mucosa during absorption may show a higher availability after administration in conventional dosage forms than in slow-release forms, because of capacity-limited biotransformation. This may explain why the apparent bioavailability of chlorpromazine in man is significantly less after administration of a prolonged-release capsule than after administration of a liquid or tablet dosage form of the drug.[48]

Drugs that are efficiently absorbed only in the proximal intestine should not be administered in a prolonged-release product. The consequence of this approach would be incomplete absorption.

PARENTERAL MEDICATION

Intramuscular Injections

There has been interest for many years in using the slow absorption of insoluble material in a muscle depot as a means of attaining prolonged drug

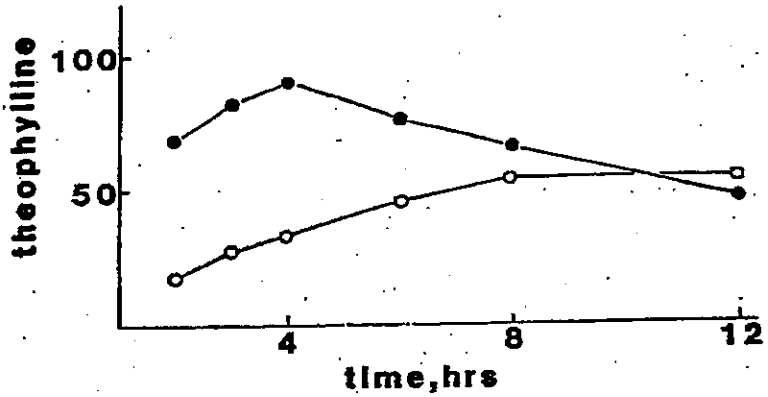

Fig. 7–8. Theophylline concentrations in serum (μmol/L) after a single dose of a prolonged-release product to fasted (●) and fed (○) children. (Data from Pedersen, S.[48])

action. Unlike oral prolonged-release dosage forms, parenteral therapy is not restricted in frequency of administration to once or twice a day. Therefore, these dosage forms can be administered weekly, monthly, or even less frequently. Sterile aqueous suspensions of insoluble salts of penicillin G, such as procaine penicillin G and benzanthine penicillin G, are available for intramuscular injection. These preparations are administered less frequently than injectable solutions of potassium penicillin G. Another long-acting intramuscular penicillin preparation consists of procaine penicillin G suspended in peanut or sesame oil, thickened with aluminum monostearate. Poorly water-soluble esters of prednisolone, testosterone, estradiol, medroxyprogesterone, and fluphenazine are also given as intramuscular injections in the form of aqueous suspensions.

Desoxycorticosterone (DOC) is a mineralocorticoid used as replacement therapy in chronic primary adrenocortical insufficiency. Therapy is initiated with intramuscular DOC acetate (DOCA). Once the maintenance dosage is established, a long-acting, microcrystalline, aqueous suspension of DOC pivalate may be used. The usual intramuscular dose of the pivalate is 25 mg for each mg of the daily maintenance dose of DOCA, repeated at 4-week intervals.

Dexamethasone is a fluorinated derivative of prednisolone used primarily in inflammatory or allergic conditions. Dexamethasone acetate is available as a long-acting repository suspension for intramuscular injection. Long-acting intramuscular formulations of methylprednisolone acetate, prednisolone acetate, triamcinolone acetonide, and triamcinolone diacetate are also available.

Androgens are used for replacement therapy in hormone-deficiency states in men and for certain gynecologic conditions and metastatic breast cancer in women. Androgens or anabolic steroids are also used in certain cases to increase growth.

Testosterone itself is not suitable for therapeutic use, except perhaps topically or by means of subcutaneous implants, because it is subject to rapid hepatic metabolism. This problem is overcome by using testosterone esters that are hydrolyzed to testosterone in the body. The esters are dissolved in oil and injected intramuscularly.

In general, the longer the hydrocarbon chain of the ester substituent, the more slowly is testosterone released into the systemic circulation. The most common esters of testosterone are the propionate, cypionate, and enanthate. Testosterone propionate is usually injected several times a week, but the longer-acting cypionate and enanthate esters need be given every 2 to 4 weeks. These longer-acting esters are drugs of choice for hypogonadism, which requires long-term therapy.

A slow-release intramuscular preparation of a luteinizing-hormone releasing-hormone (LHRH) agonist, formulated in microcapsules designed to release 100 μg/day, has also been described.[52] This preparation, administered once a month, was effective in patients with advanced ovarian and advanced prostatic carcinoma.

Failure to take medication frequently complicates the management of chronic schizophrenia. Fluphenazine decanoate and enanthate are injectable phenothiazine esters that can be administered at intervals of 1 to 3 weeks or longer for treatment of schizophrenia. In contrast, fluphenazine hydrochloride is given orally, 1 to 4 times a day. These poorly water soluble esters are prodrugs and are converted to fluphenazine upon dissolution in the body. The times required, after intramuscular injection in the dog, for 50% of the dose to be excreted in the urine and feces is 7.8 days for the enanthate ester and 22.6 days for the decanoate ester.[53] Dogs were protected against the emetic effects of a 40 μg/kg iv dose of apomorphine for 46 days after being given fluphenazine enanthate and for 105 days after a single dose of the decanoate.[53] Studies in human subjects indicate that absorption from the muscle depot occurs with a half-life of about 3 to 4 days for the decanoate ester.[54] Clinical studies with fluphenazine decanoate indicate that long-acting antipsychotic medication significantly reduces the tendency of chronic psychotic patients to discontinue treatment.[55]

The usual practice of giving fluphenazine decanoate every 2 weeks is primarily based on custom; several lines of evidence suggest that it may be given less frequently. Investigators have studied the persistence of fluphenazine levels in plasma in patients stabilized for at least 1 year on fluphenazine decanoate, 12.5 mg intramuscularly every 2 weeks.[56] Patients were randomized to either continued treatment or placebo injections every 2 weeks for 12 weeks.

No patient relapsed during the study. Mean plasma fluphenazine at baseline for all subjects was 0.86 ng/ml. For the first 6 weeks after withdrawal of the depot medication there was no statistically significant difference in fluphenazine levels be-

tween the continued treatment and placebo groups. The investigators suggested that 2-week intervals between injections of fluphenazine decanoate are excessive and that wider intervals (e.g., 3 to 4 weeks) may achieve similar clinical results.

Haloperidol decanoate, a depot form of the most widely used antipsychotic drug, is also available. The preparation is a sesame oil solution containing the equivalent of 50 mg haloperidol per ml. It is administered by deep injection into the gluteus muscle, usually at monthly intervals. After injection there is slow transfer of the ester from the lipid carrier to the aqueous medium of the tissue. Esterases in muscle tissue and plasma split the ester, releasing haloperidol.

The apparent half-life of haloperidol after depot injection is about 3 weeks. Half-life in this case reflects the release rate of the drug from the muscle depot rather than the rate of metabolism of haloperidol. Steady state occurs after 3 to 4 months of treatment. Short periods of oral haloperidol supplementation may be needed to treat reemergent psychotic symptoms until steady state is reached.

Haloperidol decanoate is intended to be used in patients stabilized on oral haloperidol. An important issue is the relationship between the intramuscular dose and the daily oral dose. As with all neuroleptics, the lowest effective dose is sought to avoid extrapyramidal side effects.

After oral administration, haloperidol is subject to first-pass metabolism; bioavailability is estimated at 60 to 70%. The bioavailability of the intramuscular depot form is probably complete. Based on relative bioavailability and frequency of dosing, a 20-fold conversion is appropriate when switching from oral haloperidol (daily dose) to haloperidol decanoate (dosed every 28 days). Clinical studies suggest that the depot form of the drug may allow even greater dose sparing.[57]

Patients with chronic schizophrenia, stabilized on oral halperidol, were switched to haloperidol decanoate, administered every 4 weeks. The first dose was determined by psychiatric history and the oral dose of haloperidol needed to stabilize the patient. Thereafter, the patient's dose could be adjusted upward or downward at 4-week intervals. For the 30 patients completing the study, the ratio of haloperidol decanoate to oral haloperidol required to achieve equal efficacy ranged from 10:1 to 15:1, lower than the 20:1 ratio needed to maintain equivalent blood levels of haloperidol. These results suggest that by reducing the variability in blood level of a drug, we may be able to achieve equal efficacy with less drug.

Estrogens and progestins are prescribed to mimic or accentuate the biologic effects of endogenous hormones: to supplement inadequate endogenous production, to correct hormonal imbalance, to reverse an abnormal process, and for contraception. Estradiol is the principal and most biologically potent ovarian estrogenic hormone. It is usually given intramuscularly in the form of an ester (benzoate, cypionate, or valerate) in oil or in an aqueous suspension. Duration of effect varies from several days to several weeks depending on the ester and formulation.

Intramuscular progestin products include a sesame-oil solution of hydroxyprogesterone caproate, used for menstrual disorders (duration of action is about 9 to 17 days), and an aqueous suspension of medroxyprogesterone acetate (MPA), used for endometriosis and injected every 3 months.

Several intramuscular depot preparations are under investigation for use as contraceptives. One preparation that is widely used throughout the world (but not in the U.S.) is depot MPA. The contraceptive use of depot MPA has been controversial for more than a decade. The drug is used in 80 countries and its use in developing nations is endorsed by scientific panels of the World Health Organization and other international agencies. The U.S. Food and Drug Administration has repeatedly denied approval of a 3-month depot MPA product for use as a contraceptive, concluding that the potential adverse effects (carcinogenicity and teratogenicity) of the drug outweigh its benefits.

Another depot progestin, norethindrone enanthate, is also used outside the U.S. for contraceptive purposes. An injection schedule calling for the first four injections to be given at 8-week intervals and subsequent injections to be given at 12-week intervals produced no pregnancies in 295 women over about 1,600 women months.[58]

Implants

The technology supporting the use of drug implants is well established but commercially successful clinical applications have been slow in coming. Numerous devices have been described for the diffusion of steroids through silicone rubber. For example, contraceptive devices in the form of silicone-rubber capsules containing progesterone have been implanted subcutaneously. Silicone-rubber capsules containing ethinyl estradiol have

been used in the treatment of patients with prostate cancer. Certain disorders of male reproductive function can be treated with long-acting implants of testosterone.

Many investigators are now applying the principles of prolonged release from silicone rubber and other polymers for long-term drug treatment. Examples include systems for narcotic antagonists, such as naloxone, in the treatment of opiate addiction, chemotherapeutic agents for the treatment of cancer, and heparin in the treatment of abnormal blood clotting.

A subdermal silastic implant containing levonorgestrel has been described. The capsules are implanted into a woman's upper or lower arm with a hypodermic needle. Within 24 hr, enough drug is released from the invisible yet palpable implant to prevent pregnancy. The capsules are said to be effective for 5 years. They can be removed if the woman wishes to become pregnant.

The generic osmotic pump, described earlier in this chapter, is a particularly useful implant for experimental drug studies in animals. The device can be implanted in the subcutaneous tissue, muscle, or peritoneal cavity. A catheter can be attached for localized administration to areas remote from the site of implantation. Commercially available pumps permit constant-rate drug delivery over 1 or 2 weeks. Publications to date have illustrated the use of the generic osmotic pumps for delivering many drugs and chemicals in various animals including mice, rats, rabbits, dogs, monkeys, sheep, and cows.[9]

Refillable implants have also been described.[59] These devices have been used in patients prone to thrombophlebitis and pulmonary embolism who require heparin. Ordinarily, heparin is given to outpatients by subcutaneous injection 4 to 6 times a day. One refillable implant delivers heparin solution continuously over 45 days before refilling is necessary. These implants have also been used to provide an intra-arterial infusion of 5-fluorouracil for the treatment of hepatoma and primary liver cancer. Recent reports describe refillable implants for the delivery of insulin[60] and antiarrhythmic drugs.[61]

A patient with refractory congestive heart failure was treated, on an outpatient basis, with intermittent dobutamine using a totally implantable infusion pump. Dobutamine was infused for 48 hr every week and resulted in sustained clinical improvement.[62]

The Food and Drug Administration has approved the use of an implantable pump to deliver the aminoglycoside antibiotic amikacin directly to the site of an osteomyelitis infection.

Battery-powered pumps were implanted in patients for phase I and II trials of low-dose continuous-infusion doxorubicin or vinblastine. The median duration of pump function was 145 days. The systems infused drugs for about 60% of their patient implant time. During 27.5 patient-years of implantation, no failure of pump mechanism was observed and pump accuracy was within 2% of stated standards. Complications requiring a second surgical procedure occurred in 24% of the patients.[63]

Remote-controlled insulin pumps were implanted into insulin dependent type I diabetics for a 1-year feasibility trial in four centers.[64] The total observation time was about 18 patient-years. Only 3 of 20 pumps had to be removed prematurely. Patients self-monitored blood glucose levels with a mean of 5.5 measurements per day. About 63% of these measurements were in the normal range. On the average, 3.25 glucose measurements per patient-month were in the hypoglycemic range and 2.6 episodes of hypoglycemia with symptoms were reported per patient-month, but very few of these episodes required medical attention. The investigators concluded that despite some technical and clinical problems, the pump, when used with a stable insulin preparation, was an effective means of treating insulin-dependent patients.

OCULAR MEDICATION

Drug effects in the eye tend to be short-lived because of the eye's efficient mechanisms to maintain homeostasis. Ocular inserts intended to release drug slowly, in a controlled fashion, offer the potential benefits of a dramatic decrease in the frequency of dosing, more uniform clinical response, and a decrease in adverse effects.

One device, called the Ocusert, containing pilocarpine, is used for lowering elevated ocular pressure. The patient places the insert under the eyelid, where it remains for 7 days, slowly and continuously delivering pilocarpine. In contrast, pilocarpine eye drops are usually instilled 3 or 4 times daily; high concentrations of the drug after dosing may produce blurring or dimming of vision for as long as 1 hr.

The Ocusert consists of the drug enclosed by a dense membrane. The detailed physical chemistry

of this system is described elsewhere.[65] Pilocarpine dissolves in the membrane and diffuses slowly to the eye. The total dosage delivered by a single Ocusert system over its 7-day lifetime is about one eighth of the amount provided by the usual 2% eye drops of pilocarpine.

Studies in the rabbit show that pilocarpine levels in ocular tissue rise and fall within each 6-hr interval between eye drops but remain relatively constant over a 2- to 8-day period with the Ocusert system (Fig. 7–9).[66] Clinical studies comparing pilocarpine eye drops with the Ocusert found comparable reductions in intraocular pressure, but 36 of the 40 patients preferred the Ocusert.[67] Another comparative study concluded that the Ocusert pilocarpine system presents many advantages and is a desirable method of therapy in selected cases of glaucoma.[68] Advantages of the device include therapeutic effectiveness, less effect on accommodation, less miosis, and convenience for the patient. Some disadvantages were the need for instruction and encouragement of the patient, retention difficulties, occasional discomfort, and higher cost.

INTRAUTERINE DEVICES

Intrauterine devices (IUDs) for contraceptive purposes are available in medicated and unmedicated forms. Medicated devices contain a diffusible contraceptive agent and are claimed to provide greater efficacy than an unmedicated device of the same size and design.

A device containing progesterone (Progestasert) releases small quantities of hormone at a uniform rate (65 μg/day) into the endometrial cavity, resulting in glandular atrophy and a chronic decidual reaction that is unfavorable for implantation; progesterone may also directly inhibit sperm. The device requires yearly replacement but devices containing a larger amount of progesterone have been found to produce effective contraception for 2 years or more.[49] Progestasert contains an amount of progesterone equivalent to the progestational agent contained in merely a half a dozen birth control pills. The product clearly illustrates the principle of using controlled-release technology to determine duration of drug effect; progesterone itself has a half-life of less than 1 hour.

TRANSDERMAL MEDICATION

Transdermal medication is intended to be applied to the skin but to elicit systemic effects. Compared to oral drug therapy, transdermal therapy has the potential advantages of avoiding biochemical degradation in the gastrointestinal tract and presystemic metabolism in the gut wall and liver, and of being able to provide long periods of drug action for relatively short-acting drugs.

Certain factors limit the application of rate-controlled transdermal drug delivery. The most im-

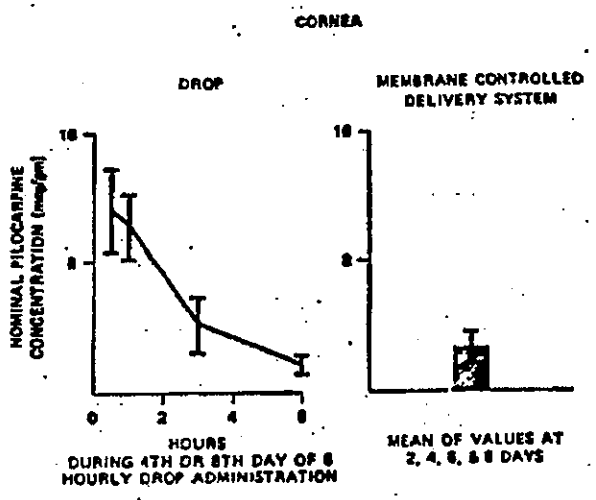

Fig. 7–9. Pilocarpine concentrations in cornea with eye-drop administration of 2% pilocarpine nitrate every 6 hr (left panel) or with a 20 μg/hr membrane-controlled pilocarpine delivery system (right panel). (From Sandelbeck, L., Moore, D., and Urquhart, J.[66] Published with permission from The American Journal of Ophthalmology, 80:274–283, 1975. Copyright by the Ophthalmic Publishing Company.)

portant one is the need for potent drugs. Existing technology is limited to drugs active at daily parenteral doses of 15 mg or less.

Transdermal scopolamine was the first transdermal system approved in the U.S. with label specifications of rate-controlled delivery. It is indicated for the prevention of motion sickness. The transdermal system is contained in a thin disk that the patient places on intact skin, usually behind the ear. The unit has multiple layers including a backing membrane, a drug reservoir consisting of solid drug suspended in a liquid vehicle, a microporous rate-controlling membrane, and a skin contact adhesive.

Scopolamine is a well-known antiemetic drug; however, it causes undesirable side effects when given in conventional tablets. These side effects appear to be related to the wide fluctuations in scopolamine concentrations in blood that occur between doses. The transdermal scopolamine system is applied only once every 3 days and provides relatively constant blood levels of scopolamine over this period.

The transdermal product delivers 0.5-mg scopolamine over 3 days. A priming quantity of 140 μg of drug is released at an asymptomatically declining rate over 6 hr, stabilizing at a maintenance rate of 5 μg/hr for the remainder of the 3-day period.

Efficacy of transdermal scopolamine has been compared with oral dimenhydrinate and placebo.[70] The transdermal device was applied 13.5 to 15 hr before exposure to motion; oral medication was given 1.5 hr before motion, and again 2.5 hr after motion began. In one study, directly comparing transdermal scopolamine with oral dimenhydrinate, the transdermal medication protected 79% of the subjects from motion sickness, whereas the oral drug protected 58%; in a second study, protection rates of 68% and 41% were found for the scopolamine and dimenhydrinate therapy, respectively. No patient was protected by the placebo.

Another study examined the influence of the time between application and exposure to motion on the efficacy of the transdermal system. Application 16 hr before motion resulted in a 100% protection rate; application 4 hr before motion protected 74% of the participants. Dry mouth, drowsiness, and blurred vision, typical side effects of scopolamine, were minimal with the transdermal system.

Other investigators have found that transdermal scopolamine is significantly more effective in preventing motion sickness induced by a ship-motion simulator than is placebo or orally administered meclizine (25 mg), a commonly used antihistamine/antinauseant.[71] A patch containing either placebo or active drug was applied behind the ear 12 hr before exposure to the simulator, and meclizine or placebo tablet was taken 2 hr before exposure. The trial lasted 90 min or until vomiting was imminent.

About two-thirds of the patients receiving transdermal scopolamine had no symptoms compared with 33% given oral meclizine and 39% given placebo. Dryness of mouth was reported more frequently with scopolamine than with meclizine or placebo. No other side effects were notable. Transdermal scopolamine may be the treatment of choice for motion sickness, but the patch must be applied at least several hours before motion to obtain optimal effect.

Several transdermal nitroglycerin systems have been marketed for the treatment of angina pectoris. These systems are more convenient to use than nitroglycerin ointment, permit more precise dosing, and need be applied less frequently than the ointment. All are intended to be applied to the upper arm or chest once a day. They should not be applied to the distal part of the extremities because bioavailability may be decreased.

Chien et al.[72] applied three commercially available nitroglycerin patches to freshly excised abdominal skin from young hairless mice and determined skin-penetration kinetics. They found that the amount of nitroglycerin delivered through the skin over 24 hr was similar for each transdermal system, ranging from 3.3 to 3.5 mg.

Other investigators measured the bioavailability of nitroglycerin from a reformulated transdermal system (Nitro-Dur II) relative to the original product (Nitro-Dur) in healthy male subjects.[73] The apparent dose of nitroglycerin delivered to each subject by each formulation was calculated from the difference between the original content of the patch and the residual nitroglycerin content after 24 hr of skin contact.

The mean total amounts of nitroglycerin delivered by the original product (I) and Nitro-Dur II were similar, 9.8 mg and 10.7 mg, respectively. Large differences in delivery, however, were observed in individual subjects; only 2.5 mg nitroglycerin was delivered from the original formulation in one subject, whereas in another subject the same formulation delivered 19.3 mg. The new for-

mulation in the same two subjects delivered 7.4 and 14.4 mg nitroglycerin, respectively. Transport through the skin rather than release from the dosage form is the rate-limiting step in the transdermal absorption of nitroglycerin. Differences among subjects reflect differences in skin permeability.

Transdermal nitroglycerin was conditionally approved by the Food and Drug Administration for the prevention and treatment of angina pectoris due to coronary artery disease. Blood level measurements demonstrating nitroglycerin concentrations in plasma similar to concentrations produced by nitroglycerin ointment, a product with established efficacy, was largely the basis for approval. According to the FDA, conditional approval reflects a determination that the drug may be marketed, while further investigations of its effectiveness are undertaken. At this time, the FDA has not made a final determination.

The evidence to date suggests rather serious shortcomings of the once-a-day nitroglycerin patch mostly related to nitrate tolerance, a well-known phenomenon. Many studies using transdermal nitroglycerin in patients with angina or congestive heart failure that have demonstrated effectiveness within several hours of application of the transdermal system, have also documented the attenuation or absence of effects within 12 to 24 hr. Other studies have suggested that complete tolerance may develop in a short time during continuous once-a-day administration of a nitroglycerin patch.[74]

A comprehensive analysis of the published clinical literature on transdermal nitroglycerin systems for the treatment of angina concluded that the patch delivering 10 mg per 24 hr is not effective at 24 hr after application.[75] This conclusion supports the hypothesis that nitroglycerin's effect on exercise tolerance is attenuated by nitrate tolerance even though blood levels persist.

A randomized controlled trial in more than 400 men with chronic stable angina showed that continuous use of transdermal nitroglycerin 5 mg/24 hr had no advantage over placebo in terms of efficacy (anginal attack rates and sublingual nitroglycerin consumption) or quality of life (as measured by a sickness impact profile and a health index of disability).[76] Patients receiving nitroglycerin reported headaches more frequently than patients on placebo and a higher proportion of them withdrew from the trial for this reason.

The future of transdermal nitroglycerin is uncertain. Current trends suggest that the dosage form will continue to be used but in doses of 10 mg/24 hr or higher, applied intermittently with a nitrate-free period (e.g., 12 hr on, 12 hr off) rather than continuously. A rest period between applications may restore sensitivity and overcome tolerance. Several studies have produced results supporting this hypothesis.[74]

Clonidine is an effective centrally-acting antihypertensive drug, but oral therapy requires administration 2 to 4 times a day and is associated with a relatively high incidence of adverse effects. Transdermal clonidine was developed with the aim of reducing frequency of administration to once weekly and with the hope of reducing side effects.

One multicenter trial evaluated weekly application of transdermal clonidine patches in patients with mild essential hypertension (diastolic blood pressure in the range of 91 to 104 mm Hg).[77] Of the 85 patients completing the trial, 54 responded (diastolic pressure < 90 mm Hg or a decrease in diastolic pressure of at least 10 mm Hg). Among the responders, 31% required one patch (releasing clonidine at a rate of 0.1 mg/day), 54% required two patches, and the other 19% needed three.

Dry mouth and drowsiness, typical side effects of clonidine, occurred in about one-third of the patients, but these symptoms were usually mild and only two subjects had to be dropped because of side effects. Of far greater concern, erythematous skin reactions were observed in 8 patients. This report and others suggest a frequency of skin reactions considerably higher than that encountered with oral clonidine. This problem may limit the use of transdermal clonidine.[78]

Most postmenopausal women who require estrogen-replacement therapy use oral medication. With this approach, however, the liver is exposed to relatively high concentrations of estrogen; increased production of coagulation factors, renin substrate, and bile acids may occur. These changes may account for the increased incidence of venous thrombosis and pulmonary embolism, hypertension, and gallstones in women treated with estrogens. This concern stimulated interest in the administration of estrogens in a way that minimizes hepatic exposure and led to the development of transdermal estradiol.

A patch releasing either 50 or 100 μg estradiol per day was approved in the U.S. for the treatment of postmenopausal symptoms but not for the prevention of osteoporosis. Transdermal estradiol may

be useful in this regard but the evidence is not yet available. The advantages claimed for the patch over oral estrogens are that estradiol goes directly to the blood (avoiding gastrointestinal effects, first-pass hepatic metabolism, and stimulation of hepatic enzymes), doses are much lower, and serum concentrations more closely resemble those found naturally before menopause.[79]

The dosage unit consists of a drug reservoir, a rate-controlling membrane, and an adhesive layer. It is intended to be applied to the trunk (but not the breasts) twice weekly. Like other estrogens for postmenopausal symptoms, the patches are generally used in cycles such as 3 weeks on and 1 week off and require the additional administration of a progestin to reduce the risk of endometrial hyperplasia and subsequent complications.

Transdermal estradiol appears to be as effective as much higher doses of oral estrogen in treating postmenopausal vasomotor symptoms, but whether the patches will be safer remains to be determined. The most common adverse effect observed with transdermal therapy has been mild to moderate erythema at the application site. This may be related to the formulation rather than to the drug itself because the problem occurs with both active and placebo patches.

BUCCAL MEDICATION

A transmucosal controlled-release formulation, containing 1, 2, or 3 mg of nitroglycerin, is available in the U.S. for both acute treatment and long-term control of angina pectoris. The product contains nitroglycerin impregnated in an inert cellulose polymer matrix. When the tablet is placed in the buccal cavity between the upper lip and gum, or between the cheek and gum, a gel forms that makes the tablet adhere to the mucosal surface, and drug slowly diffuses from the formulation to saliva and across the mucosal membranes to the systemic circulation.[80]

Onset of effects occurs in minutes and nitroglycerin continues to be absorbed as long as the tablet remains intact, usually about 4 to 5 hours. Treadmill studies in patients with angina found beneficial effects for up to 5 hours when the tablet remained intact for 5 to 6 hours. If continuous nitroglycerin therapy is desired, the next tablet should be taken within 1 hour after the previous tablet dissolves. Tolerance has not been reported with up to 2 weeks' use of transmucosal nitroglycerin, possibly because intermittent use produces a rapid rise and fall in plasma and tissue nitroglycerin levels with a nitrate-free interval at night when no medication is taken.[80]

The analgesic effects of buccal and intramuscular morphine were compared in patients who experienced pain after elective orthopedic surgery.[81] Each patient simultaneously received a buccal tablet and an injection, only one of which contained morphine. Tablets were moistened, to facilitate adherence to the mucosa, and placed between the upper lip and gum. They dissolved slowly, over about 6 hr. Efficacy was evaluated over an 8-hr period.

Seven of the 20 patients given buccal morphine required a second dose within 8 hours of the first dose; 10 of the 20 patients receiving intramuscular morphine required a second dose. As judged by the reduction in pain score, both preparations produced a similar degree of postoperative analgesia. Concentrations of morphine in plasma were lower after buccal morphine but persisted for a longer time than morphine levels after injection. The investigators suggested that this may be a useful dosage form in the management of postoperative pain.

RECTAL MEDICATION

No prolonged-release rectal dosage forms are commercially available. The generic osmotic pump, described earlier in this chapter, however, has been administered rectally in several pharmacokinetic studies in human subjects.

In one study,[82] healthy subjects inserted an osmotic pump containing antipyrine. The system remained in place in the lower rectum with a small thread attached to it and fixed to the buttock, unless there was a need to defecate. In this case, the system was pulled out, cleaned, and reinserted immediately after defecation. After 38 hr, the first system was replaced by a second which stayed in the rectum for an additional 60 hr. The constant-release rate from the osmotic pump gave rise to constant blood levels of antipyrine over a 24- to 90-hr period. This approach may be an alternative to constant rate intravenous infusion for steady state studies.

The effects of relatively constant plasma levels of triazolam, a rapidly eliminated benzodiazepine, were studied in young healthy male subjects to determine whether tolerance to certain effects may develop over a relatively short period of time.[83] The drug was given over a period of 30 hr (2 days

and 1 night) at a zero-order rate using a rectal osmotic pump. The investigators concluded that the experimental design might prove useful in the study of tolerance to drugs.

The utility of an osmotic rectal drug delivery system as a tool in steady-state pharmacokinetic interaction studies has been investigated using the cimetidine-antipyrine interaction.[84] Antipyrine was given by means of a rectal osmotic pump releasing the drug at a zero-order rate of 15 mg/hr for about 30 hr. By consecutive use of three of these systems, antipyrine was administered for 90 hr. Forty-eight hr after the start of the study, when steady state had been achieved, 400 mg cimetidine was given orally followed by three consecutive 200-mg cimetidine doses every 2 hr. The investigators concluded that the osmotic rectal drug delivery system is a useful tool in pharmacokinetic interaction studies because it provides constant steady-state concentrations, permitting investigation of the time course of drug interactions.

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EXHIBIT 23

Clinical Pharmacokinetics

Concepts and Applications

third edition

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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8

MOVEMENT THROUGH MEMBRANES

OBJECTIVES

The reader will be able to:

1. Define passive and facilitated diffusion, active transport, and permeability.
2. Distinguish between perfusion rate-limited and permeability rate-limited passage of drugs through membranes.
3. Describe the role of pH in the movement of drug through membranes.
4. Describe the consequences of the reversible nature of movement of drugs through membranes.

So far in the book, emphasis has been placed on kinetic events following drug administration and application of pharmacokinetic principles to the design and evaluation of dosage regimens. Little has been said about how underlying physiologic processes control pharmacokinetic parameters, yet such information provides an insight into the interrelationships between drug and body. It also lays a foundation for individualization of drug therapy, the subject of the next section.

This section explores the physiologic concepts basic to pharmacokinetics. It begins with a chapter dealing with the passage of drugs through membranes, proceeds through the processes of absorption, distribution and elimination, and ends with a chapter on the integration of kinetics and physiologic concepts. Such information helps not only to interpret pharmacokinetic data, obtained under a variety of circumstances, but also to predict the likely outcome when pharmacokinetic parameters change.

Absorption, distribution, and elimination are all processes that require movement through membranes. This movement is known as drug transport. The anatomic and physiologic factors that determine the rapidity of drug transport are the substance of this chapter.

TRANSPORT PROCESSES

Cellular membranes appear to be composed of an inner, predominantly lipoidal, matrix covered on each surface by either a continuous layer or a lattice work of protein (Fig. 8–1, upper section of drawing). The hydrophobic portions of the lipid molecules are oriented toward the center of the membrane and the outer hydrophilic regions face the surrounding aqueous environment. Narrow aqueous-filled channels exist between some cells as in capillary membranes and intestinal epithelia.

The transport of drugs is often viewed as movement across a series of membranes and spaces which, in aggregate, serve as a "functional" macroscopic membrane. The cells and interstitial spaces that lie between the gastric lumen and the capillary blood and the struc-

tures between the sinusoidal space and the bile canaliculi in the liver, as well as the skin (Fig. 8–1), are examples. Each of the interposing cellular membranes and spaces impede drug transport to varying degrees, and any one of them can rate-limit the overall process. In the skin, the stratum corneum is the major site of impedance. It is this complexity of structure that makes quantitative extrapolation of drug transport from one membrane to another difficult. A description of the qualitative features of the processes of drug transport across these "functional" membranes follows.

Diffusion and Convection

Most drugs pass through membranes by *diffusion*, the natural tendency for molecules to move down a concentration gradient. Movement results from the kinetic energy of the molecules, and since no work is expended by the system, the process is known as *passive diffusion*.

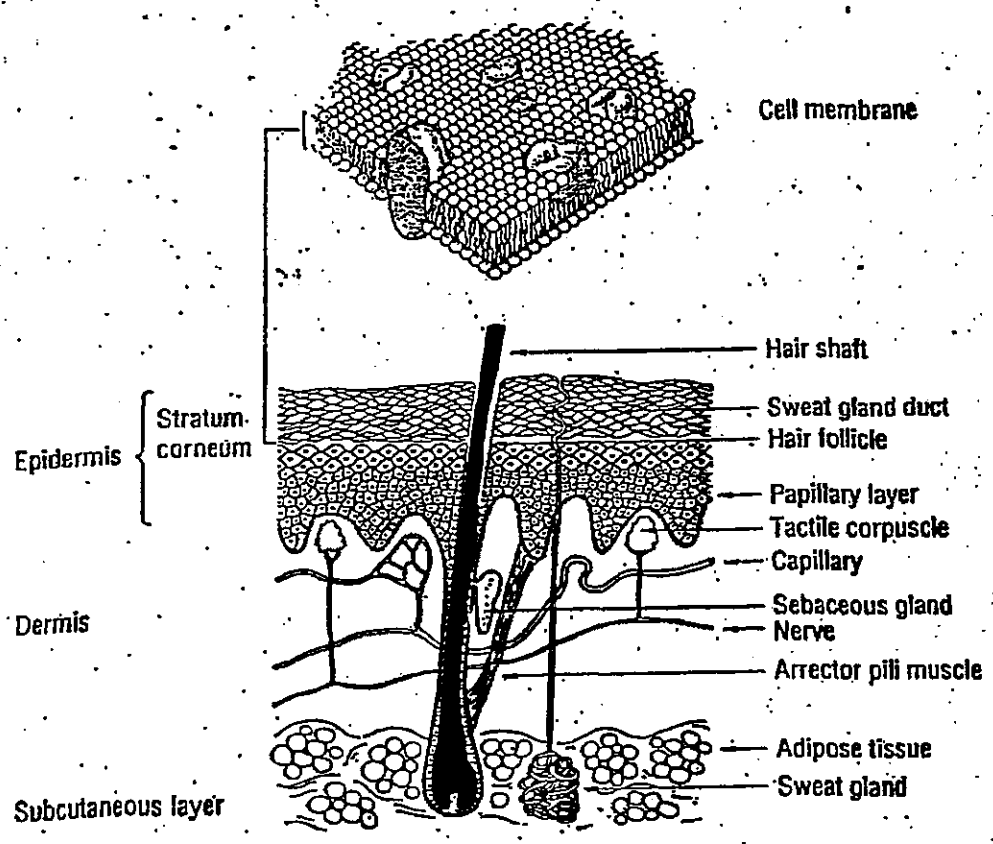

Fig. 8–1. Functional membranes vary enormously in structure and thickness. They can be as thin as a single-cell membrane, of approximately 1×10^{-6} cm thickness (top), to as thick as the multicellular barrier of the skin. This multicellular barrier extends from the stratum corneum to the upper part of the papillary layer of the dermis, adjacent to the capillaries of the microcirculation; a distance of approximately 2×10^{-2} cm (bottom). The cell membrane comprises a bimolecular leaflet, with a lipid interior and a polar exterior, dispersed through which are globular proteins, depicted as large solid irregular shaped bodies (Cell membrane—reproduced from Singer, S.J. and Nicolson, G.L.: The fluid mosaic model of the structure of cell membranes: *SCIENCE*, 175:720, 1972, copyright 1982 by the AAAS; skin was kindly drawn by Mandy North.)

To appreciate the properties of passive diffusion consider a simple system in which a membrane separates two well-stirred aqueous compartments. The driving force for drug transfer is the concentration of the diffusing species in each of the compartments on either side of the membrane. The net rate of penetration is

$$\text{Net rate of penetration} = \underbrace{P}_{\text{Permeability}} \cdot \underbrace{SA}_{\text{Surface area}} \cdot \underbrace{(C_{side1} - C_{side2})}_{\text{Concentration difference}} \quad 1$$

The importance of the surface area of the membrane is readily apparent. For example, doubling the surface area doubles the probability of collision with the membrane and thereby increases the penetration rate twofold. Some drugs readily pass through a membrane, others do not. This difference in ease of penetration is quantitatively expressed in terms of the *permeability*. Note that the product $P \cdot SA$ has the units typical of flow, volume/time. Permeability therefore has units of velocity, distance/time.

The three major sources of variation in permeability of a given membrane to a drug are molecular size, lipophilicity, and charge. Molecular size has little impact on diffusion of substances in water but has a major effect on movement through membranes. This is presumably related to the structure of membranes. For some membranes, water-soluble materials move paracellularly through narrow channels between cells. Here again, molecular size is important, as are shape and charge of the molecule. For example, oxytocin, a cyclic monopeptide, paracellularly crosses the relatively loosely knit nasal membranes quite rapidly but is almost totally unable to cross the more tightly knit gastrointestinal membranes. Movement of water through the paracellular channels (a convective process) aids in the transport of substances by this route. The second source of variation, lipophilicity, is often characterized by partition between oil and water. Small lipid-soluble un-ionized drugs tend to penetrate lipid membranes with ease. This tendency and the effect of molecular size are shown in Fig. 8–2 for transdermal passage of a variety of uncharged molecules. Charge is the third major constraint to transmembrane passage. Again, there is considerable variation in the impedance of different membranes to charged molecules, but the effect of the charge is, with few exceptions (e.g. capillary membranes), always large.

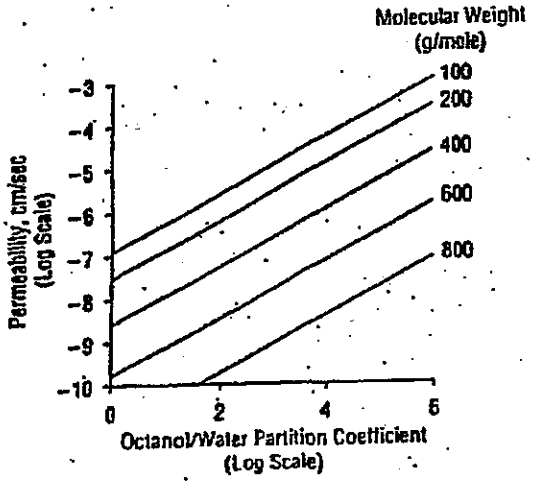

Fig. 8–2. Permeability across skin as a function of molecular size and lipophilicity. Lipophilicity is expressed as the octanol/water partition coefficient. Each line represents substances of the same molecular weight but different lipophilicity. (Modified from Potts, R.O. and Guy, R.H.: Predicting skin permeability. Pharm. Res., 9:663–669, 1992. Reproduced with permission of Plenum Publishing Corporation.)

Thus, the larger and more polar a molecule, the slower is its movement across membranes. Movement is slowed even more if the molecule is charged.

Another determinant of permeability is membrane thickness, the distance a molecule has to traverse from the site of interest (e.g., an absorption surface) to a blood capillary. The shorter the distance, the higher is the permeability. This distance can vary from about 0.005 to 0.01 μm (for cell membranes) to several millimeters (at some skin sites, Fig. 8–1, lower figure).

Drug transport continues toward equilibrium, a condition in which the concentrations of the diffusing species are the same in the aqueous phases on both sides of the membrane. Movement of drug between regions still continues at equilibrium, but the net flux is zero. Equilibrium is achieved more rapidly with highly permeable drugs, when there is a large surface area of contact with the membrane, and when the volumes of the compartments, to and from which the drug is transported, are small.

Initially, when all the drug is placed on one side of the membrane, it follows from Eq. 1 that rate of drug transport is directly proportional to concentration (Fig. 8–3). For example, rate of transport is increased twofold when concentration of drug is doubled. Stated differently, each molecule diffuses independently of the other, and the system cannot be saturated. Unless a drug alters the nature of the membrane, the last statement also applies when the other molecule is a different drug. Both absence of competition between molecules and lack of saturation are characteristics of passive diffusion.

Carrier-Mediated Transport

Membranes are not inert barriers; they have a specialized function. Membranes maintain the internal cellular environment by excluding or removing some materials and sequestering or selectively retaining vital substances. Many of these compounds are polar, with low lipid solubility. Yet they penetrate membranes much faster than anticipated for passive diffusion through an inert lipoidal barrier. Specialized carrier-mediated transport systems appear to be responsible. The substrates are often endogenous compounds, or close analogs.

The concept of a carrier stems from the observation of a limited rate of transport at increased substrate concentrations (Fig. 8–3). Two types of specialized transport processes have been proposed, passive facilitated diffusion and active transport.

Passive facilitated diffusion is exemplified by the movement of glucose into erythrocytes. It is a passive process; glucose moves down a concentration gradient without expenditure of energy, and at equilibrium, the concentrations in and surrounding the red blood cells are equal. At high plasma glucose concentrations, however, the rate of transport of glucose

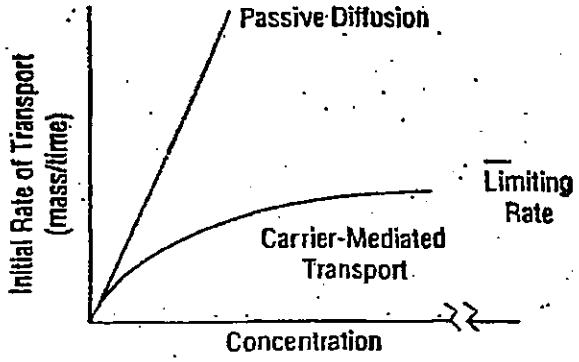

Fig. 8–3. Initial rate of drug transport is plotted against the concentration of drug placed on one side of a membrane. With passive diffusion, the rate of transport increases linearly with concentration. With carrier-mediated transport, the rate of transport approaches a limiting value at high concentrations.

into the erythrocyte reaches a limiting value or *transport maximum*. Furthermore, in common with other carrier-mediated systems, glucose transport is reasonably specific and is inhibited by other substrates. Few drugs undergo passive facilitated diffusion. An example is the transport of vitamin B_{12} across the gastrointestinal epithelium.

Examples of *active transport* abound and include renal and biliary secretion of many acids and bases, secretion of certain acids out of the central nervous system, and intestinal absorption of some amino-β-lactam antibiotics and angiotensin-converting enzyme inhibitors via the dipeptide transport system. Characteristics in common with passive facilitated diffusion are saturability, specificity, and competitive inhibition. Active transport is distinguished from passive facilitated diffusion by the net movement of substance against a concentration gradient, which can be large. The maintenance of this gradient requires metabolic energy. Active transport can therefore be impeded by metabolic inhibitors.

BLOOD FLOW

Blood, perfusing tissues, delivers and removes substances. Accordingly, viewing any tissue as a whole, the movement of drug through membranes cannot be divorced from perfusion considerations. Perfusion is usually expressed in units of mL/min per volume (or mass) of tissue.

When membranes offer virtually no barrier, the slowest or rate-limiting step is perfusion, not permeability, as shown in Fig. 8–4. This perfusion limitation is exemplified in Fig. 8–5 for the passage of certain substances across the jejunal membranes of a rat, from lumen to blood. Tritiated water moves freely through the membrane, and its rate of passage increases with increasing perfusion. The passage of ethanol and many small drugs across the small intestine is similarly perfusion rate-limited.

As membrane resistance to drug increases, the rate limitation moves away from one of perfusion to one of permeability. The problem now lies in penetrating the membrane, not in delivering drug to, or removing it from, the tissue (Fig. 8–4B). This increase in resistance may arise for the same drug crossing membranes of increasing thickness; e.g., the multiple cell layers of the epidermis are less permeable to a drug than is the single cell layer of the capillary epithelium. For the same membrane, resistance increases with increasing size and polarity of the molecule. Thus, transport across the jejunum is slower for ribitol and many

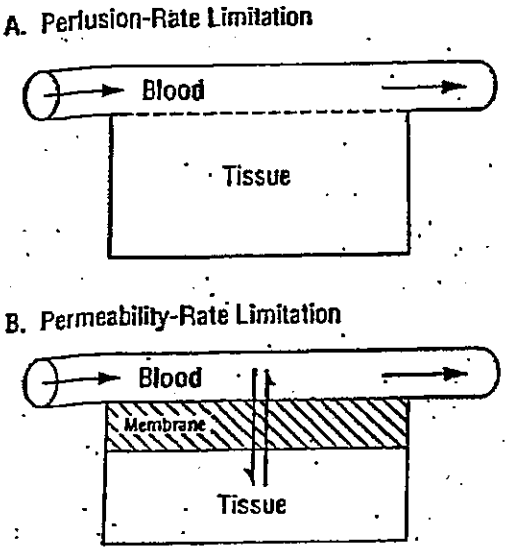

Fig. 8–4. The limiting step controlling rate of movement of drug across a membrane, from blood to tissue or the converse, varies. *A*, If the membrane offers no resistance, drug in the blood leaving the tissue is in virtual equilibrium with that within tissues; blood and tissue may be viewed as one. Here movement of drug is limited by blood flow. *B*, A permeability-rate limitation exists if membrane resistance to drug movement becomes high; movement here is both slow and insensitive to changes in perfusion. Also, equilibrium is not achieved by the time the blood leaves the tissue; blood and tissue must now be viewed as separate compartments.

other larger polar compounds than for ethanol or water, which results in insensitivity to changes in perfusion (Fig. 8–5).

Some compounds, like urea, have intermediate permeability characteristics across the jejunum. At low blood flow rates, the compound has sufficient time to traverse the membrane so that perfusion becomes rate-limiting. At higher blood flow rates, however, membrane permeability becomes the rate-limiting step, and absorption becomes relatively insensitive to blood flow (Fig. 8–5).

IONIZATION

Most drugs are weak acids or weak bases and exist in solution as an equilibrium between un-ionized and ionized forms. Increased accumulation of drug on the side of a membrane where pH favors greater ionization of drug has led to the *pH partition hypothesis*. According to this hypothesis, only un-ionized nonpolar drug penetrates the membrane, and at equilibrium, the concentrations of the un-ionized species are equal on both sides.

The majority of evidence supporting the pH partition hypothesis stems from studies of gastrointestinal absorption, renal excretion, and gastric secretion of drugs. The pH of gastric fluid varies between 1.5 and 7.0; urine pH fluctuates between 4.5 and 7.5. Elsewhere in the body, changes in pH tend to be much smaller and to show less deviation from the pH of blood, 7.4.

The un-ionized form is assumed to be sufficiently lipophilic to traverse membranes. If it is not, theory predicts that there is no transfer, irrespective of pH. The fraction un-ionized is controlled by both the pH and the *pKa* of the drug according to the Henderson-Hasselbalch equation. Thus, for acids,

$$pH = pKa + \log_{10}\left(\frac{\text{Ionized concentration}}{\text{Un-ionized concentration}}\right) \qquad 2a$$

and for bases

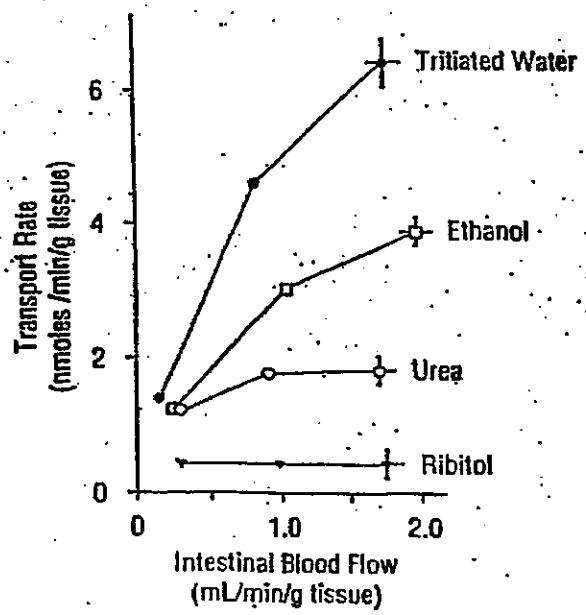

Fig. 8–5. The rate of passage of a substance across the jejunum of a rat was determined by measuring its rate of appearance in intestinal venous blood. The passage is blood flow limited when, like tritiated water, the molecule freely permeates the membrane. With poorly permeable substances, like the polar molecule ribitol, the passage is limited by transmembrane penetration, not by blood flow. (Redrawn from Winne, D., and Remischovsky, J.: Intestinal blood flow and absorption of non-dissociable substances. J. Pharm. Pharmacol., 22:640–641, 1970.)

$$pH = pKa + \log_{10}\left(\frac{\text{Un-ionized concentration}}{\text{Ionized concentration}}\right) \qquad 2b$$

As $\log_{10}(1) = 0$, the pKa of a compound is the pH at which the un-ionized and ionized concentrations are equal. The pKa is a characteristic of the drug (Fig. 8–6). Consider, for example, the anticoagulant warfarin. Warfarin is an acid with pKa 4.8, i.e., equimolar concentrations of un-ionized and ionized drug exist in solution at pH 4.8. Stated differently, 50% of the drug is un-ionized at this pH. At one pH unit higher, 5.8, the ratio is 10 to 1 in favor of the ionized drug; i.e., 10 out of 11 total parts or 91% of the drug now exists in the ionized form, and only 9% is un-ionized. At one pH unit lower than the pKa, 3.8, the percentages in the ionized and un-ionized forms are 9 and 91, the converse of those at pH 5.8.

Figure 8–7 shows changes in the percent of un-ionized drug with pH for acids of different pKa values. The pH range 1.0 to 8.0 encompasses values seen in the gastrointestinal tract and the renal tubule. Several considerations are in order and are exemplified by transport across the gastrointestinal barrier. First, very weak acids, such as phenytoin and many barbiturates, whose pKa values are greater than 7.5 are essentially un-ionized at all pH values. For these acids drug transport should be rapid and independent of pH, provided the un-ionized form is permeable. Second, the fraction un-ionized only changes dramatically for acids with pKa values between 3.0 and 7.5, and for these compounds a change in rate of transport with pH is expected and has been observed. Third, although transport of still stronger acids, those with pKa values less than 2.5, should theoretically also depend upon pH, in practice the fraction un-ionized is so low that transport across the gut membranes may be slow even under the most acidic conditions.

A similar analysis indicates that a base must be very weak, pKa less than 5, for transport to be independent of pH. Caffeine (pKa 0.8) is an example of a base that is rapidly trans-

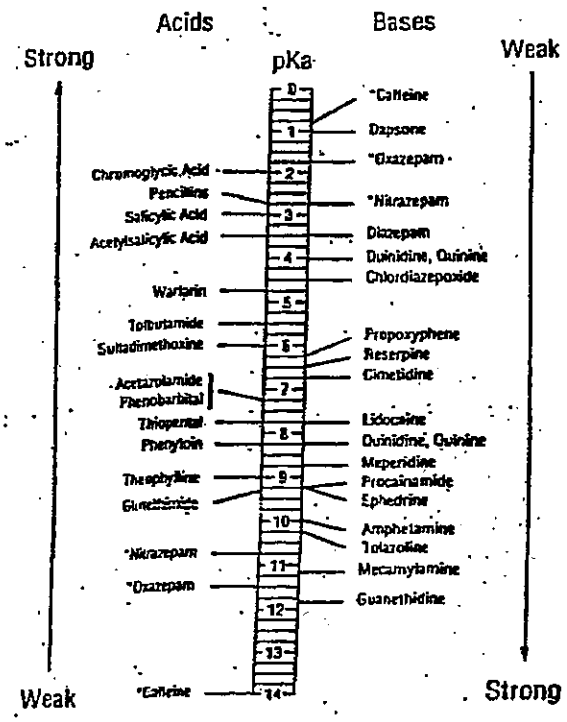

Fig. 8–6. The pKa values of acidic and basic drugs vary widely. Some drugs are amphoteric (*), i.e., they have both acidic and basic functional groups.

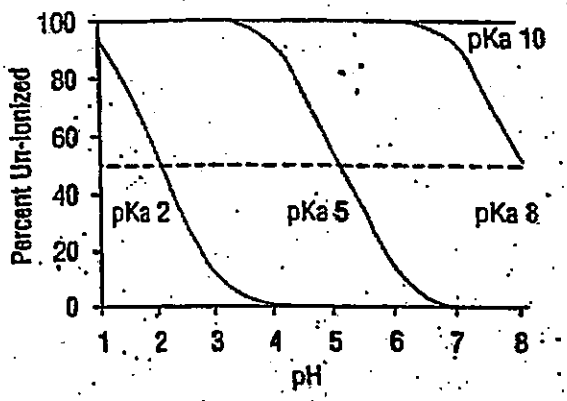

Fig. 8–7. Very weak acids, *pKa* values greater than 8.0, are predominantly (above dashed line) un-ionized at all pH values between 1.0 and 8.0. Profound changes in the fraction un-ionized occur with pH for an acid whose *pKa* value lies within the range of 2.0 to 8.0. Although the fraction un-ionized of even stronger acids increases with hydrogen ion concentration, the absolute value remains low at most pH values shown.

ported and shows no pH-dependent absorption. Only with stronger bases, those with *pKa* values between 5 and 11, is pH-dependent transport expected. At the usually low pH of the gastric fluid, these bases exist almost exclusively in the ionized form, and for these, gastric transport should be slow. Passage of these bases should be more rapid from a less acidic environment. All evidence supports these expectations.

As originally proposed, the pH partition hypothesis relates to events at equilibrium, yet it has been applied most widely to predict the influence of pH on the rates of absorption and distribution. The likely influence of pH on a rate process depends, however, on where the rate limitation lies. Only if the limitation is in permeability is an effect of pH on rate expected. If the limitation is in perfusion, the problem is not one of movement of drug through membranes and, therefore, any variation in pH is unlikely to have much effect on the rate process. Where the equilibrium lies, however, is independent of what process rate-limits the approach toward equilibrium. Accordingly, pH is predicted to affect the distribution of an ionizable drug across a membrane at equilibrium in all cases in which the membrane is permeable only to un-ionized drug.

Despite its general appeal, the pH partition hypothesis fails to explain certain observations. A variety of quaternary ammonium compounds (e.g., propantheline bromide) which are always ionized elicit systemic effects when given orally. Movement of these compounds through the gastrointestinal membranes occurs, although at a slow and erratic rate. Animal studies also indicate penetration of the ionized form of many acids and bases through membranes, though at a slower rate than the un-ionized form. These observations suggest that quantitative prediction of the influence of pH on the movement of drugs across a membrane is unlikely to be accurate.

PROTEIN BINDING

Many drugs bind to plasma proteins and tissue components (discussed in Chap. 10). Such binding is reversible and usually so rapid that an equilibrium is established within milliseconds. Consequently, the associated (bound) and dissociated (unbound) forms of the drug can be assumed to be at equilibrium at all times and under virtually all circumstances.

Only unbound drug is thought to be generally capable of passing through membranes, the protein-bound form being too large to do so. The influence of protein binding on the rate of movement through a membrane can be viewed in much the same way as that of the influence of pH on the movement of weak acids and bases. Both binding and ionization are virtually instantaneous reactions, with only one species (unbound, un-ionized form) capable of traversing membranes. If there is a perfusion limitation, dissociation of the

bound drug and diffusion of the unbound drug through the membrane must occur so rapidly that rates of delivery and transport are equal. Thus, an alteration in protein content is not expected to affect rate at a given concentration. If permeability is rate-limiting, little of the drug presented moves into the tissue. For a given rate of delivery, altered protein binding, by affecting the unbound concentration, now influences the rate of transport.

REVERSIBLE NATURE OF TRANSPORT

It is important to remember that drug transport is generally bidirectional. One tends, for example, to think of drug absorption in the gastrointestinal tract as being unidirectional. Normally, with very high concentrations of drug placed into the gastrointestinal tract, following oral administration, the net rate of transport is toward blood in mesenteric capillaries. However, important applications can be made of transport in the opposite direction. For example, repeated oral administration of charcoal can hasten removal from the body of drugs such as digoxin, phenylbutazone, phenobarbital, and digitoxin in cases of drug overdose. Because of extensive adsorption of drug to charcoal, the lumen of the gastrointestinal tract acts as a sink for removal of drug from blood. In this case, the site of transfer may be restricted to only a small region of the gastrointestinal tract or may apply to a much larger area. The restriction depends on the distribution of charcoal along the gastrointestinal tract. Even with complete distribution of charcoal, whether the overall transfer from blood to gut lumen is perfusion rate-limited or not depends on the permeability of the various functional membranes along the length of the gut as well as on blood flow to these various sites.

As previously stated, the concepts of this chapter on passage of drugs across membranes are important to an understanding of movement of drugs into, within, and out of the body. In the next three chapters, these concepts are incorporated with other principles dealing with drug absorption, distribution, and elimination.

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. Define the terms: passive diffusion, passive facilitated diffusion, active transport, and permeability.
2. How accurate are each of the following statements?
   a. When distribution is perfusion-rate limited, the ratio of concentrations across the capillary membrane of the tissue is virtually one at all times.
   b. When the surface area of a membrane is doubled, so is its permeability.
   c. Passive diffusion across a membrane stops when the concentrations on both sides are the same.
   d. Carrier-mediated transport is one in which energy is needed to transfer drug across a membrane.
   e. Protein binding in the aqueous phases diminishes the permeability of membranes.
3. Molecular size is an important determinant of permeability. Figure 8–2 summarizes the results of skin penetration for a variety of un-ionized compounds. Using the figure, describe the effect of doubling molecular weight on the permeability for a series of compounds of equal lipophilicity (octanol/water partition coefficients on log scale are all equal to 2).
4. Briefly discuss the role of ionization in the movement of weak acids and weak bases across membranes.
5. Table 8–1 shows the effect of oral administration of activated charcoal on removal of phenobarbital from the body.

Table 8-1. Effect of Repeated Doses of Activated Charcoal on the Half-life (Hours) of Phenobarbital[a]

DURING COADMINISTRATION OF ACTIVATED CHARCOAL[b]	ABSENCE OF CHARCOAL ADMINISTRATION
36 ± 13	93 ± 7

[a]Pond, S.M., Olson, K.R., Osterloh, J.D., and Tong, T.G.: Randomized study of the treatment of phenobarbital overdose with repeated doses of activated charcoal. JAMA, 251:3104-3108, 1984.
[b]17 g of charcoal in 70 ml of 70% sorbitol every 4 h administered through a nasogastric tube.

a. Knowing that the volume of distribution of phenobarbital is 0.55 L/kg, calculate the clearance of phenobarbital into the alimentary canal during treatment with charcoal. Hint: CL (during treatment) = CL (no treatment) + CL (by charcoal).
b. The clearance value determined in "a" should apply as well to movement of drug from the lumen of the gastrointestinal tract into the bloodstream. If the majority of drug removal and absorption occurs in the small intestine, estimate the half-life associated with absorption when 0.4 L of fluid is in the small intestine. For this problem, conceive the small intestine as a single compartment.

9

ABSORPTION

OBJECTIVES

The reader will be able to:

1. Describe the steps involved in the oral absorption of a drug.
2. Distinguish between dissolution and permeability rate-limitations in absorption.
3. Anticipate the influence of physicochemical properties of a drug on its absorption from different sites of administration.
4. Anticipate the role of gastric emptying and intestinal transit in the gastrointestinal absorption of a drug, with particular reference to the physicochemical properties of the drug and its dosage form.
5. List the factors influencing dissolution rate of a drug.
6. Describe the influence of decreased permeability and surface area along the intestinal tract on the performance of oral constant-rate release systems *in vivo*.

Drugs are most frequently administered extravascularly. The majority are intended to act systemically, and for these, absorption is a prerequisite for activity. Delays or losses of drug during absorption may contribute to variability in drug response and, occasionally, may result in failure of drug therapy. It is primarily in this context, as a source of variability in systemic response and as a means of controlling the concentration-time profile of drug in the body, that absorption is considered here and throughout the remainder of the book. It should be kept in mind, however, that even for those drugs intended to act locally (e.g., mydriatics, local anesthetics, nasal decongestants, topical agents, and aerosol bronchodilators), movement of drug from the site of application to the systemic circulation influences time of onset, intensity, and duration of effect.

This chapter deals with the general principles governing rate and extent of drug absorption. Although absorption from other sites is discussed, emphasis is placed on absorption following oral administration. This is not only because the oral mode of administration is the most prevalent for systemically acting drugs, but also because it illustrates many sources of variability encountered in drug absorption.

Figure 9–1 depicts the numerous steps involved in the absorption of a drug given orally. Being a complex structure, many anatomic and physiologic factors affect the overall rate and extent of drug absorption from the gastrointestinal tract, making a precise quantitative prediction difficult. Nonetheless, much can be understood and appreciated of the events occurring at this and other sites of absorption.

Absorption is favored because the body acts as a large sink. A concentration gradient is present until virtually no drug remains to be absorbed. The gradient is maintained longer, the larger the volume of distribution of the drug.

Passage of drug through the membranes dividing the absorption site from the blood is a prerequisite for absorption to occur. To do so, the drug must be in solution. Most drugs are administered as solid preparations. Common examples are tablets and capsules. Because solid particles cannot pass through membranes, a drug must dissolve to be absorbed. Many factors influence the release of drug from a solid pharmaceutical formulation. *Biopharmaceutics* is a comprehensive term denoting the study of the influence of pharmaceutical formulation variables on the performance of a drug *in vivo*.

ABSORPTION FROM SOLUTION

Several physiologic and physical factors that determine movement of drug through membranes have been discussed generally in Chap. 8. Included among them are the physicochemical properties of the molecule, the nature of the membrane, perfusion, and pH. These factors and others are now considered with respect to drug absorption.

Gastrointestinal Absorption

In accordance with the prediction of the pH partition hypothesis, weak acids are absorbed more rapidly from the stomach at pH 1.0 than at pH 8.0, and the converse holds for weak bases. Absorption of acids, however, is always much faster from the less acidic small intestine (pH 6.6 to 7.5) than from the stomach (Fig. 9–2). These apparently conflicting observations can be reconciled. Surface area, permeability, and for perfusion rate-limited absorption, blood flow are important determinants of the rapidity of absorption. The intestine, especially the small intestine, is favored on all accounts. The total absorptive area of the small intestine, composed largely of microvilli, has been calculated to be about 200 M^2, and an estimated 1 L of blood passes through the intestinal capillaries each minute. The corresponding estimates for the stomach are only 1 M^2 and 150 mL/min. The permeability

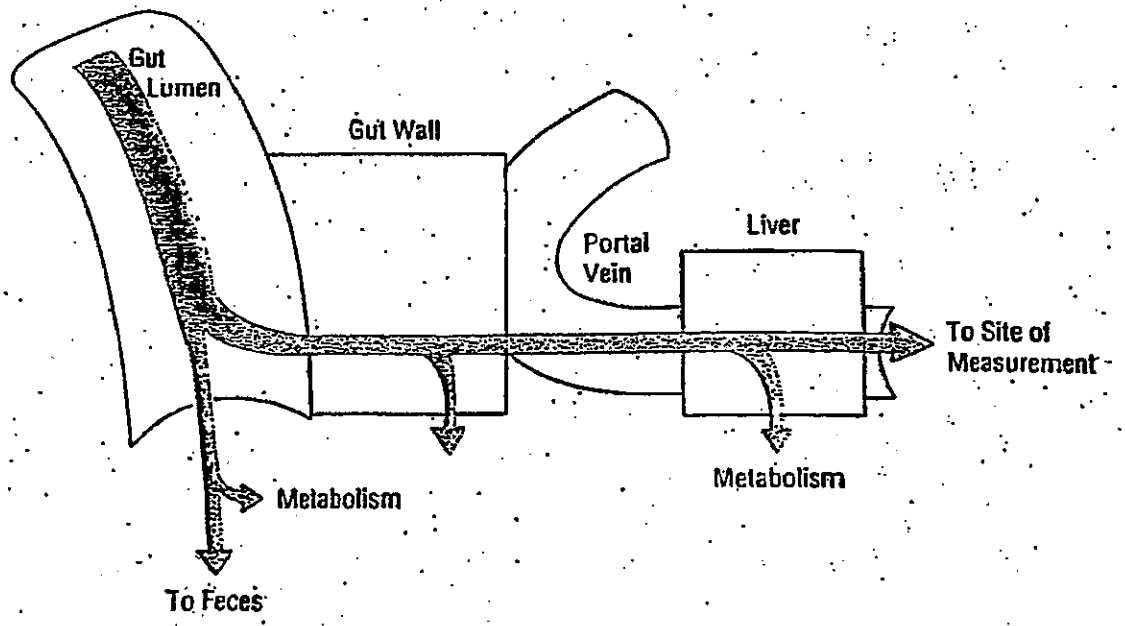

Fig. 9–1. A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement during gastrointestinal absorption. Dissolution, a prerequisite to movement across the gut wall, is the first step. Incomplete dissolution or metabolism in the gut lumen or by enzymes in the gut wall is a cause of poor bioavailability. Removal of drug as it first passes through the liver further reduces bioavailability.

of the intestinal membranes to drugs may also be greater than that of the stomach. These increases in surface area, permeability, and blood flow more than compensate for the decreased fraction of un-ionized acid in the intestine. Indeed, the absorption of *all* compounds, be they acids, bases, or neutral compounds, is faster from the (small) intestine than from the stomach. Because absorption is greater in the small intestine, the rate of gastric emptying is a controlling step in the speed of drug absorption.

Gastric Emptying. Gastric emptying of liquids is approximately zero-order. Food, especially fat, slows gastric emptying, which explains why drugs are frequently recommended to be taken on an empty stomach when a rapid onset of action is desired. Drugs that influence gastric emptying also affect the rate of absorption of other drugs (Fig. 9–3).

Retention of drug in the stomach increases the percentage of a dose absorbed through the gastric mucosa, but usually the majority of drug is still absorbed through the intestinal epithelium. In this regard, the stomach may be viewed as a repository organ from which pulses of drug are ejected by peristalsis onto the absorption sites in the small intestine.

Intestinal Absorption. Throughout its length, the intestine varies in its multifaceted properties and luminal composition. The intestine may be broadly divided into the small

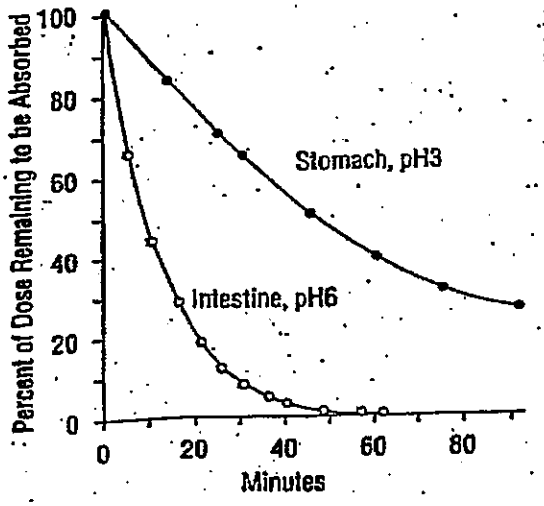

Fig. 9–2. Despite an environment favoring a greater percentage of un-ionized drug, absorption of salicylic acid (p*Ka* 3) is slower from the rat stomach at pH 3 (●) than from the rat intestine at pH 6 (○). (Modified from Doluisio, J.T., Billups, N.F., Dittert, L.W., Sugita, E.G., and Swintosky, J.V.: Drug absorption I. An *in situ* rat gut technique yielding realistic absorption rates. J. Pharm. Sci., 58:1196–1199, 1969. Adapted with permission of the copyright owner.)

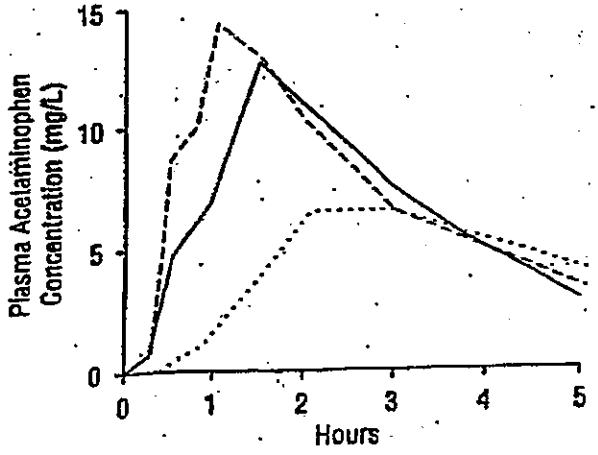

Fig. 9–3. Slowing gastric emptying by propantheline (30 mg i.v.) slows the rate of absorption of acetaminophen (1500 mg), administered orally in a 22-year-old male, as seen by a decrease in the maximum plasma concentration and a longer time to reach this concentration (·····) compared to values when acetaminophen is given alone (———). Metoclopramide (10 mg i.v.), which hastens gastric emptying, hastens the absorption of acetaminophen (– – –) (1 mg/L = 6.6 μM). (Redrawn from Nimmo, J., Heading, R.C., Tothill, P., and Prescott, L.F.: Pharmacological modification of gastric emptying: Effects of propantheline and metoclopramide on paracetamol (acetaminophen) absorption. Br. Med. J., 1:587–588, 1973.)

and large intestine separated by the ileocecal junction. Surface area per unit length decreases from the duodenum to the rectum. Electrical resistance, a measure of the degree of tightness of the junctions between the epithelial cells, is much higher in the colon than in the small intestine. Proteolytic and metabolic enzymes, as well as active and facilitated transport systems are distributed along the intestine, often in restrictive regions. The colon abounds with anaerobic microflora. The mean pH, 6.6 in the proximal small intestine rising to 7.5 in the terminal ileum, falls sharply to 6.4 at the start of the cecum before finally rising to 7.0 in the descending colon. Transit time of materials is around 3 to 4 hr in the small intestine and from 10 to 24 hr or even longer in the large bowel. Although these and other complexities make precise quantitative prediction of intestinal drug absorption difficult, several general features emerge.

The permeability-surface area product ($P \cdot SA$) tends to decrease progressively from duodenum to colon. This applies to all drug molecules traversing the intestine epithelium by non carrier-mediated processes, whether via the transcellular or paracellular route. The decrease in $P \cdot SA$ is seen as a decrease in the kinetics of absorption when drugs are placed in different parts of the intestine, as illustrated in Fig. 9–4 for ranitidine.

Permeability in the small intestine can be sufficiently high so that absorption from the lumen is perfusion rate-limited (Fig. 8–5, p. 114). Under these conditions, overall gastric emptying would rate-limit absorption from an oral solution. As shown in Fig. 8–5, at any one site along the intestine, in this case the jejunum, small molecules permeate more freely than larger ones. The issue of molecular size is particularly important for polar drugs. These substances move paracellularly via the tight functions between epithelial cells. Permeability appears to drop off sharply with molecular weights above 350 g/mole. Molecular size has

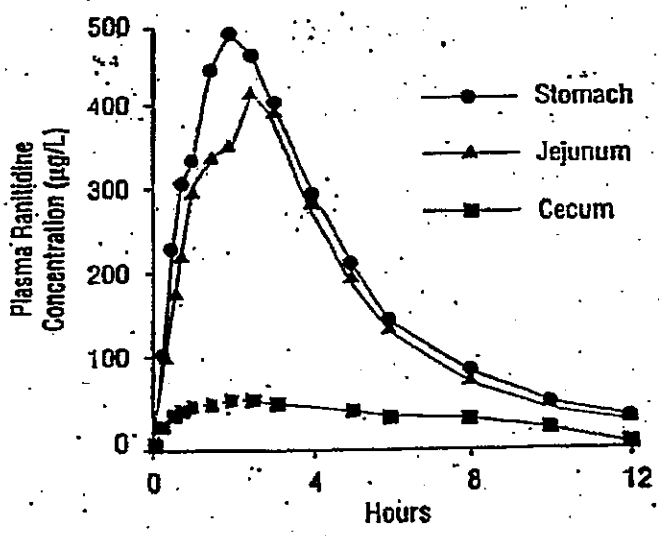

Fig. 9–4. The gastrointestinal absorption of ranitidine varies with site of application. Shown are the mean plasma concentration-time profiles of ranitidine observed after placing an aqueous solution (6 mL) containing 150 mg of ranitidine hydrochloride into the stomach (●), jejunum (▲), and colon (■) of eight volunteers, via a nasoenteric tube. The much less extensive absorption of this small (M.W. = 313 g/mole) polar molecule from the colon is consistent with the idea that the permeability-surface area ($P \cdot SA$) product is much lower in the colon than in the small intestine. Notice that absorption of ranitidine effectively ceases (in terminal decline phase) by 3 hr when placed in the stomach or jejunum, even though the drug is incompletely bioavailable ($F \sim 0.6$, data not shown) suggesting that the small intestine is the major site of absorption when rantidine is taken orally. (Adapted from Williams, M.F., Dukes, G.E., Heizer, W., Han, Y-H., Hermann, D.J., Lampkin, T., and Hak, L.J.: Influence of gastrointestinal site of drug delivery on the absorption characteristics of ranitidine. Pharm. Res., 9:1190–1194, 1992.)

less of an effect on permeability for lipophilic drugs, which trasverse transcellularly. The ultimate limit to permeability is size, however. Thus, large polypeptides, proteins, and other macromolecular drugs are virtually unable to pass through the intestine wall even if they are metabolically stable, unless they can be processed by one of the specialized systems that traffic vital materials, such as vitamin B_{12}, from the apical to the basolateral surface of the epithelial cell.

Causes of Low Oral Bioavailability. When a drug is given in solution and passes readily across membranes; absorption from most sites of administration is complete. This is not always so, especially when drugs are placed into the gastrointestinal tract.

A drug must pass sequentially from the gastrointestinal lumen, through the gut wall, and through the liver, before entering the general circulation (Fig. 9–1). This sequence is an anatomic requirement because blood perfusing virtually all gastrointestinal tissues drains into the liver via the hepatic portal vein. If the only cause of loss is incomplete time for absorption, then the bioavailability is less than one and the complement, the fraction appearing in feces unchanged, is a measure of luminal retention. Drug may also be lost by decomposition in the lumen; the fraction entering the tissues, F_F, is then the fraction neither lost in the feces nor decomposed in the lumen. Of this permeating drug, only a fraction may escape destruction within the walls of the gastrointestinal tract, F_G, thereby reducing the fraction of dose reaching the portal vein to $F_F \cdot F_G$. If drug is also eliminated in the liver, an additional fraction, F_H, of that reaching the liver escapes extraction there. The measured overall systemic bioavailability, F, clearly is then

$$F = F_F \cdot F_G \cdot F_H \qquad (1)$$

For example, if 50% of the drug is lost at each step, the bioavailability of the drug, measured systematically, would be $0.5 \times 0.5 \times 0.5$ or 12.5%. Note that the drug can be rendered totally unavailable at any one of these steps.

The lungs are excluded from the foregoing considerations of bioavailability even though they may occasionally be an important site of elimination. As discussed in Chap. 4, drug given intravenously is used as a standard to measure bioavailability, with calculation based on measurement of drug at a peripheral venous site. Both intravenously and orally administered drugs must first pass through the lungs to reach this site of measurement. Consequently, the effect of the lungs on the measurement of bioavailability need not be considered.

Insufficient Time for Absorption. The $P \cdot SA$ term for drugs appears to drop sharply with movement from the small intestine to colon. How much of this drop is due to a decrease in permeability and how much to a decrease in surface area between small and large intestine is not known for certain. For permeable drugs, absorption is rapid and probably complete within the small intestine. Even if some drug were to enter the large intestine, the permeability there would still be sufficiently high to ensure that all that entered was absorbed. Absorption of less permeable, generally polar, drugs still primarily occurs within the small intestine but is unlikely to be complete within the limited 2- to 4-hr transit period. Evidence supporting this notion is provided with the H_2-antagonist ranitidine. This relatively polar stable compound is almost totally excreted unchanged when given intravenously. When given orally, 60% is absorbed but all within the first 3 to 4 hr after administration (Fig. 9–4); the rest is recovered unchanged in feces. Evidently, very little ranitidine is absorbed from the large intestine even though drug can be there for up to 24 hr.

Table 9–1 lists representative drugs for which oral bioavailability is very low (0.1 to 14%), most likely due to poor intestinal permeability with most of that absorbed having occurred within the small intestine. The drugs share the common properties of being polar

and, with the exception of pyridostigmine, relatively large (molecular weight greater than 400 g/mole). Pyridostigmine is a quaternary ammonium compound, which may explain its low bioavailability despite its small molecular weight (181 g/mole). Most of the compounds listed in Table 9–1 cannot be given orally for effective systemic activity; they must be given parenterally.

Finally, there are small molecular weight, 200 to 350 g/mole, polar drugs for which absorption, although incomplete (50 to 80%), is sufficiently high to render them useful given orally. These include cimetidine, ranitidine, hydrochorothiazide, and atenolol. As with ranitidine, though, the small intestine is likely to be the predominant site of absorption.

The rectum has a small surface area, and a drug given rectally is not always retained for a sufficient length of time to ensure complete absorption. No time limitation exists for a drug injected into muscle, subcutaneous tissue, and most other sites within the body; complete absorption is anticipated unless destruction occurs between site of administration and systemic circulation.

Competing Reactions. Any reaction that competes with absorption may reduce the oral bioavailability of a drug. Table 9–2 lists various reactions that can occur within the gastrointestinal tract. Reactions can be both enzymatic and nonenzymatic. Acid hydrolysis is a common nonenzymatic reaction. Enzymes in the intestinal epithelium and within the intestinal microflora, which normally reside in the large bowel, metabolize some drugs. The reaction products are often inactive or less potent than the parent molecule. Interactions with constituents of the gastrointestinal fluids also occur; the result may be low drug bioavailability. For example, one reason why tetracycline is incompletely absorbed when coadministered with milk and with certain antacids is that this antibiotic forms spar-

Table 9-1. Representative Drugs Showing Low Oral Bioavailability That Is Due to Poor Intestinal Permeability[a]

Amikacin	Gentamicin
Carbenicillin	Neomycin
Cefamandole	Pyridostigmine
Cefazolin	Streptomycin
Cefotaxime	Teicoplanin
Ceftazidime	Vancomycin

[a]Less than 20% bioavailable. Administered either in solution or as an immediate-release dosage form.

Table 9-2. Representative Reactions within the Gastrointestinal Tract That Compete for Drug Absorption From Solution

REACTION	DRUG	COMMENT
Complexation	Tetracycline	Unabsorbed insoluble complexes with polyvalent metal ions, e.g., Ca^{2+}, Al^{3+}, Fe^{3+}
Conjugation		
Sulfoconjugation	Isoproterenol	Loss of activity: product inactive
Glucuronidation	Salicylamide	Loss of activity: product inactive
Decarboxylation	Levodopa	Loss of activity: given with a peripheral dopa decarboxylase inhibitor to reduce gastrointestinal metabolism
Hydrolysis		
Acid	Penicillin G	Loss of activity: product inactive
	Erythromycin	Loss of activity: product inactive
	Digoxin	Products (digitoxides) have variable activity
Enzymatic	Aspirin	Salicylic acid formed, active anti-inflammatory compound
	Pivampicillin	Active ampicillin formed; pivampicillin (ester) is inactive
	Insulin	Loss of activity: product inactive
Oxidation	Cyclosporine	Loss of activity: product less active
Reduction (microflora)	Sulfasalazine	Intended for local (intestinal) anti-inflammatory action; parent drug may have some activity; product, 5-aminosalicylic acid, active
Adsorption	Digitoxin	Adsorption to cholestyramine; adsorbed material not absorbed

ingly soluble complexes with the polyvalent cation (e.g., Ca^{2+}, Fe^{3+} and Al^{3+}) contained in these preparations.

The complexities that occur *in vivo* preclude accurate prediction of the contribution of a competing reaction to decreased bioavailability. Sometimes the problem of incomplete absorption can be circumvented by physically protecting the drug from destruction in the stomach (see enteric coating discussion, p. 36) or by synthesizing a more stable derivative, which is converted to the active molecule within the body. Similarly, to enhance absorption, more permeable derivatives are made, which are rapidly converted to the active molecule, often during passage through the intestinal wall. For example, absorption of the polar antibiotic ampicillin is incomplete. Its systemic delivery is improved substantially by administering a more lipophilic and permeable inactive ester prodrug, pivampicillin. The hydrolysis of this ester within the intestinal wall is so rapid that only ampicillin is detected in the circulation. Derivatives, such as pivampicillin, are generally referred to as *prodrugs*, as they are pharmacologically inactive.

Hepatic Extraction. Aspirin (acetylsalicylic acid) is one of the first synthetic prodrugs. It was marketed at the turn of the century to overcome the unpleasant taste and the gastrointestinal irritation associated with the parent drug, salicylic acid. Aspirin was originally thought to be inactive, being designed to be rapidly hydrolyzed within the body to salicylic acid. Only subsequently was aspirin shown to be pharmacologically active. Yet the original design worked; upon ingestion, aspirin, a labile ester, is rapidly hydrolyzed, particularly by esterases in the liver. Indeed, hepatic hydrolysis is so rapid that a sizeable fraction of aspirin is converted to salicylic acid in a single passage through the liver, resulting in a substantial "first-pass effect."

Drugs that show a substantial first-pass effect due to hepatic elimination are listed in Table 9–3. Apart from this feature, they have little in common. They are of diverse chemical structure, possess different pharmacologic activities, and are metabolized via a number of pathways. When the metabolite(s) formed during the first pass through the liver is less potent than the parent drug, the oral dose is larger than the i.v. or i.m. dose required to achieve the same therapeutic effect. This occurs for many of the drugs listed in Table 9–3. In some instances, e.g., isoproterenol, hepatic extraction is so high as to essentially preclude the oral route. Here, no amount of pharmaceutical formulation helps. Either the drug must be given by a parenteral route, or it must be discarded in favor of another drug candidate. A method of estimating the maximum likely decrease in oral bioavailability due to this first-pass effect is discussed in Chap. 11, Elimination.

Table 9–3. Representative Drugs Showing Low Oral Bioavailability That Is Due to Extensive[a] First-Pass Hepatic Elimination[b]

Alprenolol	Hydralazine	Naltrexone
Amitriptyline	Imipramine	Neostigmine
Chlormethiazole	Isoproterenol	Nicardipine
Chlorpromazine	Isosorbide dinitrate	Nicotine
Cytarobine	Ketamine	Nifedipine
Desipramine	Labetolol	Nitroglycerin
Dextropropoxyphene	Lidocaine	Papaverine
Dihydroergotamine	Lorcainide	Phenacetin
Diltiazem	Mercaptopurine	Pentazocine
Doxepin	Methylphenidate	Pentoxifylline
Doxorubicin	Metoprolol	Propranolol
Encainide	Morphine	Scopolamine
Estradiol	Nalbuphine	Testosterone
5-Fluorouracil	Naloxone	Verapamil

[a] $f \leq 0.5$ or less, on average.
[b] Adapted and expanded from Fond, S.M., and Tozer, T.N.: First-pass elimination: Basic concepts and clinical consequences. Clin. Pharmacokinet., 9:1–25, 1984.

Avoiding first pass through the liver probably explains most of the activity of nitroglycerin administered sublingually for an acute anginal attack. Blood perfusing the buccal cavity bypasses the liver and enters directly into the superior vena cava. This antianginal drug is almost completely metabolized as it passes through the liver, and any drug swallowed is not systemically available. The metabolites seen in blood are only weakly active but under certain circumstances may reach concentrations high enough to contribute to overall activity.

The rectal route has a definite advantage over the oral route for drugs destroyed by gastric acidity or by enzymes in the intestinal wall and microflora. Potentially, the rectal route may also partially reduce first-pass hepatic loss. Part of the rectal blood supply, particularly the inferior and middle hemorrhoidal veins, bypasses the hepatic portal circulation and dumps directly into the inferior vena cava. Achieving a reproducible bioavailability, which is important in drug therapy, may be difficult, however, since bioavailability strongly depends on the site of absorption within the rectum.

Absorption From Intramuscular and Subcutaneous Sites

The General Case. In contrast to the small intestine, and indeed to the entire gastrointestinal tract, absorption of most drugs in solution from muscle and subcutaneous tissue is perfusion rate-limited; increases in blood flow hasten absorption. For example, consider the data in Table 9–4 for the local anesthetic lidocaine. Shown are the peak plasma concentrations observed when the same dose of lidocaine is administered at different sites in the body. Recall, for a given dose, the higher the peak concentration, the faster is drug absorption. Large differences in speed of absorption are clearly evident, the speed decreasing from intercostal muscle to s.c. tissue, in line with a decreasing tissue perfusion.

This dependence of absorption on perfusion may be explained by the nature of the barrier (the capillary wall) between the site of injection (interstitial fluid) and blood. This capillary wall, a much more loosely knit structure than the epithelial lining of the gastrointestinal tract, offers little impedance to the movement of drugs into blood, even for polar ionized drugs. For example, gentamicin, a water-soluble, ionized, polar base of molecular weight 477 g/mole, has great difficulty penetrating the gastrointestinal mucosa but is rapidly and completely absorbed from an intramuscular site. This low impedance by the capillary wall in muscle and s.c. tissue applies to drugs, independent of *pKa*, degree of ionization, and molecular size up to approximately 5000 g/mole.

Macromolecular and Lymphatic Transport. In contrast to small molecules, size, polarity, and charge pose a particular problem for administration of protein, and large polypeptide drugs; their transport across many membranes is hindered. Furthermore, be-

Table 9–4. Influence of Site of Injection on the Peak Venous Lidocaine Concentration Following Injection of a 100-mg Dose[a]

INJECTION SITE	PEAK PLASMA LIDOCAINE CONCENTRATION (mg/l)[b]
Intercostal	1.46
Paracervical	1.20
Caudal	1.18
Lumbar epidural	0.97
Brachial plexus	0.53
Subarachnoid	0.44
Subcutaneous	0.35

[a] Taken from Covino, B.G.: Pharmacokinetics of local anaesthetic drugs. In: Pharmacokinetics of Anaesthesia. Edited by C. Prys-Roberts and C.C. Hug. Blackwell Scientific Publications, Oxford, 1984, pp. 270–292.
[b] One mg/l = 4.3 μM.

cause of decomposition by proteolytic enzymes in the gastrointestinal tract, their oral absorption is extremely low and erratic. Most of the information on these kinds of drugs has been obtained following nonvascular parenteral administration. For the s.c., i.m., and intraperitoneal routes, drug reaches the systemic circulation by two mechanisms: diffusion through the interstitial fluids and fenestrations in the linings of the vascular capillaries and by convective flow of the interstitial fluids through lymphatic channels. Molecular size is of primary importance for passage across the capillary endothelium. Polypeptides of less than approximately 5000 g/mole primarily pass through the capillary pathway. Those of greater than about 20,000 g/mole are less able to traverse the capillary wall; they primarily enter the blood via the lymphatic pathway.

Lymph flow is slow and causes absorption from nonvascular parenteral sites to continue for many hours, as shown in Fig. 9–5 for glycosylated recombinant human granulocyte-macrophage colony-stimulating factor (molecular weight = 15,000 to 34,000 g/mole). The drug has a half-life of 68 min after i.v. administration, but following s.c. administration, the plasma concentration is prolonged for at least 42 hr, with a rate of decline indicating continuing input.

The nonvascular parenteral routes offer the advantage of providing prolonged input for short half-life proteins. Thus, nonvascular parenteral administration allows for less frequent administration than the i.v. route. A main concern here relates to the reproducibility of the release into the systemic circulation from the site of administration. Absorption kinetics from both i.m. and s.c. administration has been shown to be highly dependent on the site of injection, temperature, and degree of rubbing at the injection site.

Because of the short half-life often observed and decomposition in the gastrointestinal tract, there is clearly a need for the development of novel delivery systems for protein drugs. Smaller polypeptides have been tested in controlled-release (microencapsulated) injectable systems. They have also been shown to be absorbed across nasal membranes. Higher molecular weight polypeptides and proteins may require more creative methods to

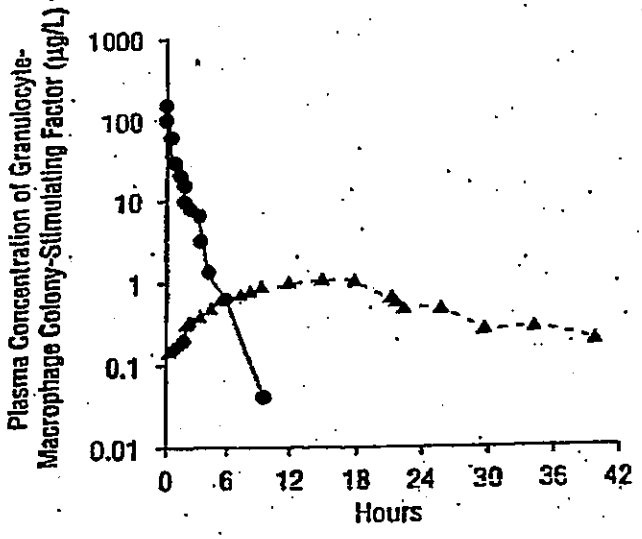

Fig. 9–5. Plasma concentrations of glycosylated recombinant human granulocyte-macrophage colony-stimulating factor following i.v. (●, solid line) and s.c. (▲, dashed line) bolus injection of 8 µg/kg. The results, obtained in two different individuals, typify the kinetics of the drug following these two modes of parenteral administration. (Adapted from Hovgaard D., Mortensen, B.T., Schifter, S., and Nissen, N.I.: Clinical pharmacokinetic studies of a human haemopoietic growth factor, GM-CSF. Euro. J. Clin. Invest., 22:45–49, 1992.)

ensure consistent and more complete bioavailability or may require the development of more specific methods for delivering these drugs to the site of action.

Absorption From Other Sites

Drugs may be administered to virtually any site of the body. This is certainly true of local anesthetics. In recent years there has been considerable interest in exploiting some of the less conventional sites, such as the lung, nasal cavity, and buccal cavity as a means of delivering drugs systemically. The new polypeptide and protein drugs that are poorly and erratically absorbed when given orally have received particular attention. Transdermal application has become popular for systemic delivery of small, generally lipophilic, potent molecules that require low input rates to achieve effective therapy. In all cases, consideration has to be given to the particular properties of the site and the drug. Nonetheless, the factors influencing absorption from these sites are likely to be the same as those influencing absorption from the oral, i.m., and s.c. sites.

ABSORPTION FROM SOLID DOSAGE FORMS

Formulation

Equality of drug content does not guarantee equality of efficacy. The presence of different excipients (ingredients in addition to drug) and manufacturing processes may result in dosage forms containing the same dose of drug behaving differently *in vivo*. Hence the reason for testing for bioequivalence of preparations of a drug intended to be switchable (p. 45). Generally, the primary concern is with the extent of absorption. Occasionally, variations in absorption rate may be important. Much often depends on the degree of accumulation that occurs on multiple dosing (Fig. 7–6, p. 87).

The major cause of differences in absorption of a drug from various products is dissolution. Standards exist for content and purity of the numerous inactive ingredients used to stabilize the drug; to facilitate manufacture and maintain integrity of the dosage form during handling and storage; and to facilitate, or sometimes control, release of drug following administration of the dosage form. Intended, or otherwise, each ingredient can influence the rate of dissolution of the drug, as can the manufacturing process. The result is a large potential for differences in drug absorption among products. Indeed, a large variety of dosage forms of drugs are marketed in which release may be immediate, delayed, prolonged, or sustained, regardless of the physicochemical properties of the drug itself. Sometimes, differences in absorption can be correlated with differences in dissolution measured in an *in vitro* apparatus. There are dissolution requirements for an increasing number of important drug products. On occasion, however, *in vitro* dissolution tests fail to correlate with absorption. At present, assessment in humans continues to be the primary means of evaluating drug products and discriminating between satisfactory and unsatisfactory formulations.

Dissolution

The reason why dissolution is so important may be gained by realizing that absorption following administration of a solid is a two-step process:

$$\text{Drug in product} \xrightarrow{\text{Dissolution}} \text{Drug in solution} \xrightarrow[\text{the body}]{\text{Entry into}} \text{Absorbed drug}$$

Two situations are now considered. The first, depicted in Fig. 9–6A, is one in which dis-

solution is a much faster process than is entry of drug into the body. Consequently, most of the drug is dissolved before an appreciable amount is absorbed. Here, permeability rather than dissolution rate-limits absorption. An example is the gastrointestinal absorption of neomycin given as a tablet. This polar antibiotic dissolves rapidly but has difficulty penetrating the gastrointestinal epithelium. So, little is absorbed. Differences in rates of dissolution of neomycin from different tablets have little or no effect on the speed of absorption of this drug.

In the second and much more common situation, shown in Fig. 9–6B, dissolution proceeds relatively slowly, and any dissolved drug readily traverses the gastrointestinal epithelium. Absorption cannot proceed any faster, however, than the rate at which the drug dissolves. That is, absorption is dissolution rate-limited. In this case, changes in dissolution profoundly affect the rate, and sometimes the extent, of drug absorption. Evidence supporting dissolution rate-limited absorption comes from the noticeably slower absorption of most drugs from solid dosage forms than from a simple aqueous solution.

Factors Controlling Dissolution

Many factors influence the dissolution of a drug. Among these are surface area, solubility, pH, and stirring.

Expanding the surface exposed to body fluids hastens dissolution. Reducing the size of the solid particles is the most common means of achieving this goal. To this effect, for example, materials (disintegrants) are incorporated into tablets that cause them to swell upon contact with water and then to disintegrate into granules that finally deaggregate into the original fine drug particles.

In dissolution rate-limited absorption, the concentration of drug in solution at the absorption site is kept low because dissolved drug rapidly enters the body. The driving force for dissolution is directly related to the solubility of the drug at the surface of the dissolving

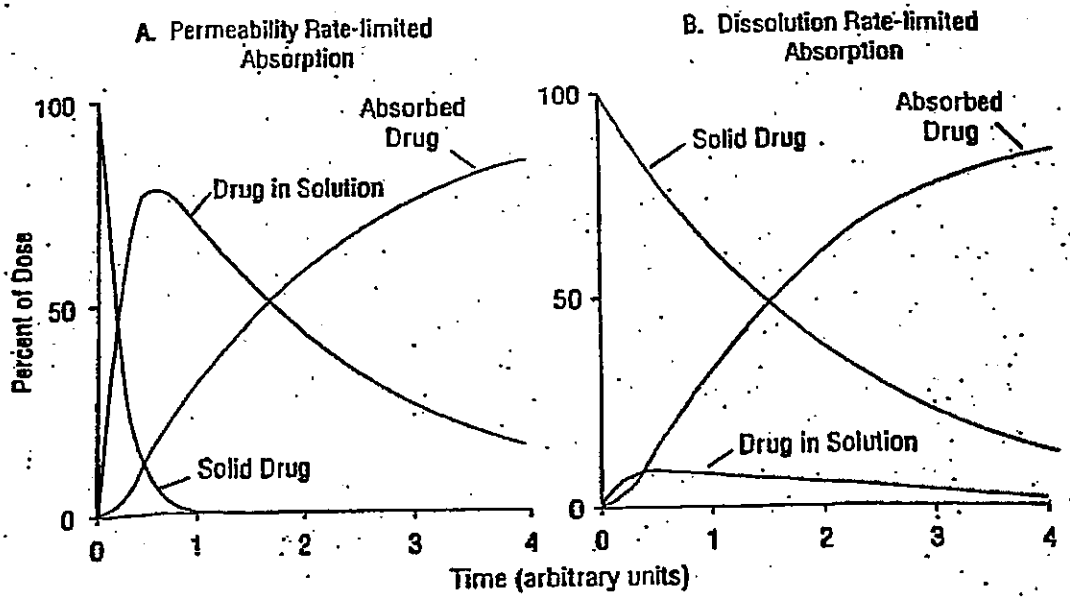

Fig. 9–6. When absorption is permeability rate-limited (Case A), most of the drug has dissolved (colored line) before an appreciable fraction has been absorbed. In contrast, when dissolution rate-limits absorption (Case B), very little drug is in solution (colored line) at the absorption site at any time; drug is absorbed as soon as it dissolves. Notice that the majority of drug not absorbed is always found at the rate-limiting step: in solution in Case A and as a solid in Case B.

solid. This explains why tablets, capsules, and even suspensions of sparingly soluble drugs are prone to absorption problems. Even if dissolution were not the rate-limiting step and a saturated solution at the absorption site could be maintained, the rate of absorption of these drugs would still be low, owing to the low aqueous solubility.

For weak acids and bases, the rate of dissolution can be markedly increased by using a salt form. The explanation lies in the different concentrations at the surface of the dissolving solid. This concentration is much higher for the much more soluble salt than for the free acid or base. Adjusting pH of the medium also increases dissolution of weak acids and bases, by helping to maintain such conditions around the dissolving material. This is generally, however, not as effective as using a salt form.

Peristaltic movements in the stomach are generally feeble and variable. Mixing in the antrum can be quite vigorous. The disintegration rate, deaggregation rate, location of the dosage form in the stomach, food, and the state of the patient each influences the stirring rate around the dissolving particle. Stirring is generally sufficient to ensure complete and rapid drug absorption from solid dosage forms containing soluble drugs.

As mentioned previously, little drug is generally absorbed from the stomach. Nonetheless, dissolution in the gastric fluid is a prerequisite to the absorption of some drugs. This point is well illustrated by tetracycline hydrochloride. Only that which dissolves in the stomach is apparently absorbed. This amphoteric antibiotic, freely soluble in both strongly acidic and alkaline solutions, is minimally soluble at pH 5.8, a pH typical of the intestinal fluid. Perhaps the sparingly soluble tetracycline precipitates onto undissolved particles entering the intestine, thereby limiting further dissolution.

Gastric Emptying and Intestinal Transit

Before discussing the role of gastric emptying on absorption of drugs given as solids, consider the information provided in Fig. 9–7. Shown are the mean transit times in the stomach and small intestine of small nondisintegrating pellets (diameters between 0.3 and 1.8 mm) and of large single nondisintegrating units (either capsules, 25 mm by 9 mm or tablets, 8 to 12 mm in diameter).

During fasting, gastric emptying of both small and large solids is seen, on average, to be rapid, with a mean transit time of around 1 hr, although there is considerable individual variability. In this state, the stomach displays a complex temporal pattern of motor activity with alternating periods of quiescence and moderate contraction of varying frequency, culminating in an intense contraction, the "housekeeping wave," that propels all gastric contents, including solids almost irrespective of size, into the small intestine. The exact ejection time of a solid particle therefore depends on when the solid is taken during the motor activity cycle, an unpredictable period varying from 20 min to a few hours.

The situation is very different after eating. As shown in Fig. 9–7, when taken on a fed stomach, the gastric transit time of solids is increased. This increase is greater after a heavy meal than after a light one and is much greater for a large single unit than for small pellets. For example, the mean gastric transit time for large single unit systems is now almost 7 hr, with some of them still in the stomach 11 hr after ingestion. These observations are explained by the sieving action of a fed stomach. The irregular "housekeeping waves" are now replaced by regular and more gentle contractions, which continuously mix and triturate the gastric contents. Furthermore, only solids with diameters less than 7 to 10 mm are allowed to pass into the small intestine with gastric fluid. Larger food particles are retained until reduced to the requisite size by trituration and partial digestion. With conventional tablets, disintegration and subsequent deaggregation into fine particles achieves the same objective. As long as the stomach remains in a fed state, the conditions above prevail. For those persons who eat three good meals a day, this is most of the waking hours of the day.

In contrast to events in the stomach, the transit time of solids within the small intestine varies little among subjects, appears to be independent of either the size of a solid or the presence of food in the stomach, and is remarkably short, approximately 3 hr (Fig. 9–7), a time similar to that found for the transit of liquids. Both solids and liquids appear to move down the small intestine as a plug with relatively little mixing. As the mouth-to-anus transit time is typically 1 to 2 days, these data on gastric and small intestinal transit times indicate that, for the majority of this time, unabsorbed materials are in either the large bowel or rectum. Provided with the physiologic information above, the possible role of gastric emptying and intestinal transit on the absorption of drugs given in solid dosage forms can be understood. Consider the following situations.

Rapid Dissolution in Stomach. This is the common situation seen with many conventional tablets and capsules. Drug dissolves so rapidly that most is in solution before much has entered the intestine. Here, gastric emptying clearly influences the rate of drug absorption. Hastening gastric emptying, for example, quickens drug absorption from solution.

Rapid Dissolution in Intestine. In this situation, drug does not dissolve in the stomach, whereas in the intestine it rapidly both dissolves and passes across the intestinal wall. Gastric emptying then dramatically affects the time and perhaps the rate of drug absorption. An enteric-coated product is an extreme example of this situation. Erythromycin and pen-

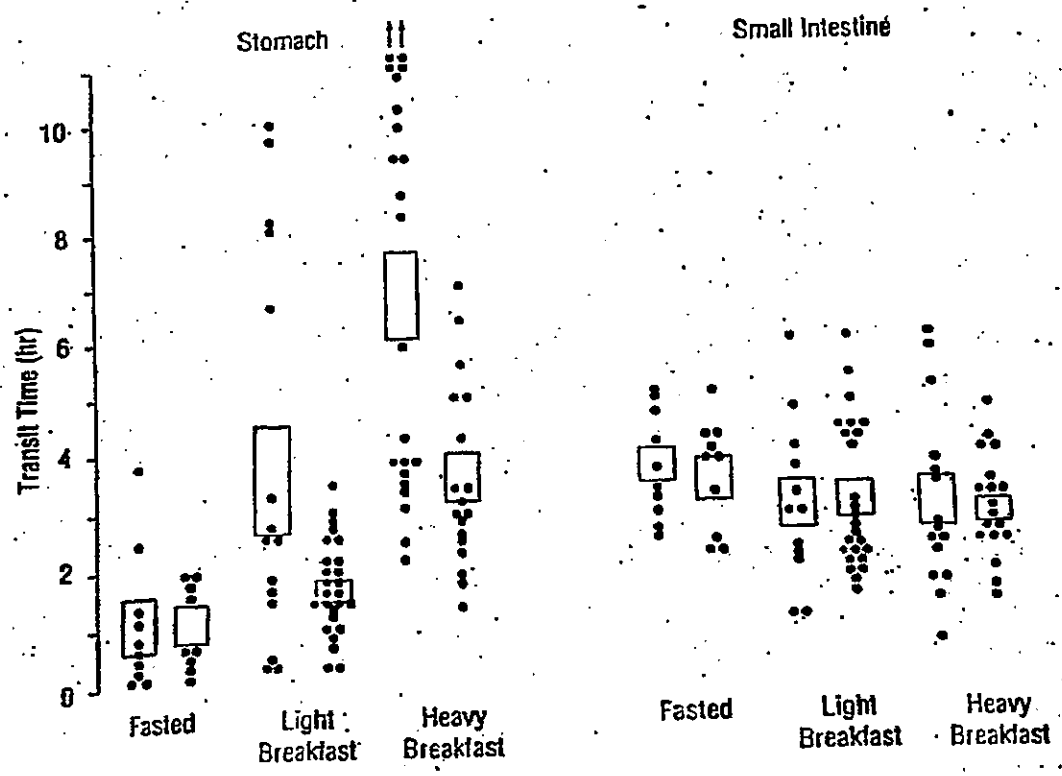

Fig. 9–7. Food, particularly a heavy meal, increases the gastric transit time of small pellets (black circles) and, even more markedly, of large single units (colored circles). In contrast, neither food nor the physical size of the solid affects the small intestine transit time. The data (individual points, black or colored circles, and their mean ± S.E., indicated by the rectangles) were obtained in healthy young adults using drug-free nondisintegrating materials. The points with an arrow indicate the solid was still in the stomach at the time of the last observation, the time indicated. (Adapted from Davis, S.S., Hardy, J.G., and Fara, J.: Transit of pharmaceutical dosage forms

icillin G are rapidly hydrolyzed to inactive products in the acidic environment of the stomach. Salicylic acid is a gastric irritant. A solution to both types of problems has been to coat these drugs with a material resistant to acid but not to the intestinal fluids. Many such enteric-coated products are large single tablets, and the time taken for an intact tablet to pass from the stomach into the intestine varies unpredictably from 20 min to several hours when taken on an empty stomach and up to 12 hr or even more when taken on a fed stomach. Accordingly, such enteric-coated products are not to be used when a rapid and reliable rate of absorption is required. A product composed of enteric-coated granules is an improvement because the rate of delivery of the granules to the intestine is expected to be more reliable, being less dependent on a single event and on food.

Poor Dissolution. Some drugs, such as the oral antifungal agent griseofulvin, are sparingly soluble in both gastric and intestinal fluids. When these drugs are administered as a solid, there may already be insufficient time for complete dissolution and absorption. With a fixed short time within the small intestine, retention in the stomach increases the time for drug to dissolve before entering the intestine, thereby favoring increased bioavailability. As mentioned, food, and fat in particular, delays gastric emptying. This delay may be one of the explanations for the observed increase in the bioavailability of griseofulvin when taken with a fatty meal or with fats. Subsequently, as the intestinal fluid and contents move into the large intestine and water is reabsorbed, the resulting compaction of the solid contents may severely limit further dissolution and hence absorption of drug.

Controlled-Release Products. The conclusions drawn for sparingly soluble drugs may also apply to certain controlled-release dosage forms. Some of these are coated with, or contained within, a nondisintegrating material through which the release rate of drug is independent of both pH and agitation. In such cases, gastric emptying has little effect on the rate of drug absorption. Even though the solid dosage form may be retained in the stomach, the released drug is continuously emptied with the gastric fluid into the duodenum and is available for absorption. Any delay in the gastric emptying of such products prolongs the total period for drug release and absorption. For reasons discussed above, this delay is most likely to be seen with large single units taken on a fed stomach. It would be unwise, however, to depend too much on this delay to achieve a prolonged absorption profile given the well-known unpredictability of patients' eating habits and their general lack of compliance in taking medications. Furthermore, some concern must exist that compaction in the large intestine may preclude reliable input of drug beyond 12 to 16 hr. This would severely limit the design of controlled-release dosage forms of drugs with short half-lives intended for once-a-day administration. That said, data for some drug-delivery systems indicate that reliable and sustained absorption for up to 22 hr can be achieved. Future work in this area is needed to understand the scope and limitations of the approach. One limitation can be the properties of the drug itself, as now discussed.

Changing Rate Control

The rate of absorption is controlled by a delivery device as long as release from the device is the rate-limiting step in the absorption process. With the $P \cdot SA$ term for drugs decreasing along the length of the intestinal tract, the rate limitation could change from the device to the intestinal membrane as the device moves down the intestine (Fig. 9–8). Much depends on the relative impedances for drug movement in the device and in the intestinal wall. In the small intestine, $P \cdot SA$ is at its highest and control may then well lie with the delivery device. However, on movement into the colon, $P \cdot SA$ may drop enough so that the rate-limiting step becomes passage across the wall, in which case, control of drug input is lost. This situation is more likely to occur with relatively polar molecules, for which permeability

may be a problem. Even with rapid-release dosage forms, absorption of these compounds is essentially restricted to the small intestine (e.g., Fig. 9–4). Currently, however, it is difficult to make any quantitative prediction of those drugs for which controlled drug delivery can be achieved beyond the small intestine. But clearly, whenever release of drug beyond the stomach continues for 4 hr or more, some of the drug is likely to be released in the large intestine (Fig. 9–7). More needs to be known about the relationship between the physicochemical properties of a molecule and intestinal permeability. Currently, the only recourse is to evaluate the drug delivery system *in vivo*.

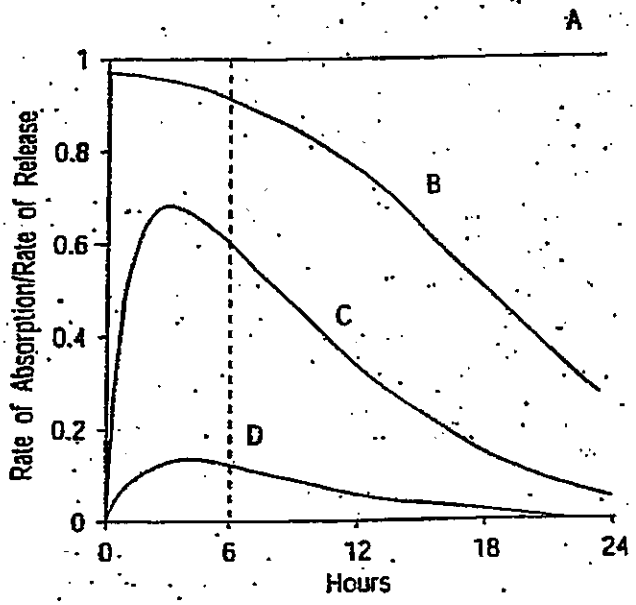

Fig. 9–8. The rate of absorption relative to the rate of constant release from an oral 24-hr sustained-release delivery device varies with time when movement across the membranes of the gastrointestinal tract, rather than release, becomes rate limiting. The change in rate control from release to membrane occurs for a drug with low membrane permeability. The rate control imposed by permeability is more apparent in the colon (6 hr is shown as the time for the device to leave the stomach and transit the small intestine, dashed vertical line), where permeability is much lower than that in the small intestine. The simulations are conducted with the model

$$\underset{\text{Net rate of change of released drug in lumen}}{\frac{dA_R/dt}{}} = \underset{\text{Rate of release}}{R} - \underset{\text{Rate of absorption}}{\frac{P \cdot SA}{Va} \cdot e^{-bt} \cdot A_R}$$

where A_R is amount of released drug residing in the gastrointestinal tract. Va is the volume of luminal fluid into which the released drug is distributed, and b is the rate constant for the decrease in $P \cdot SA/Va$ with time. As the actual changes in P, SA, and Va with time are unknown, an exponential (half-life of 3 hr) decline in the composite is used. The following conditions are simulated: **A.** $P \cdot SA/Va$ is sufficiently high (approaches ∞) to ensure that the rate-controlling step is always in the device with rate of absorption matching rate of release. **B.** $P \cdot SA/Va$ is 10 hr^{-1}, a value for which drug is absorbed virtually as quickly as it is released while in the proximal small intestine but not so further down the gastrointestinal tract where rate control by the device is lost. **C.** $P \cdot SA/Va$ is 1 hr^{-1}. The rate of absorption never matches the rate of release. The product fails to control absorption. **D.** $P \cdot SA/Va$ = 0.1 hr^{-1}. Rate control lies almost entirely with the membranes of the gastrointestinal tract at all times. In cases *B to D*, drug accumulates in the lumen of the intestines. The area under each curve relative to the area under the release curve (curve A) is the fraction of released drug that is absorbed.

Precipitation and Redissolution

Absorption is normally complete within 1 or 2 hr of i.m. or s.c. administration of an aqueous solution of a drug. There are exceptions, as seen with protein drugs (Fig. 9–5) and when injecting a solution of a salt of either a sparingly soluble acid or base. For example, although chlordiazepoxide hydrochloride, in solution, is eventually completely absorbed, absorption is slow from the i.m. site. However, large doses sometimes appear to be poorly effective or ineffective. Indeed, absorption is even slower than from the gastrointestinal tract; when capsules of chlordiazepoxide hydrochloride are administered (Fig. 9–9). The explanation involves consideration of pH; solubility, perfusion, and stirring.

In the study referenced in Fig. 9–9, the same dose, 50 mg of chlordiazepoxide hydrochloride, was administered by both routes. The i.m. dose was dissolved in 1 mL of an aqueous vehicle. Chlordiazepoxide is sparingly soluble; its aqueous solubility is approximately 2 mg/mL. To achieve this high concentration of 50 mg of chlordiazepoxide hydrochloride/mL, the vehicle contains 20% propylene glycol and 4% polysorbate 80, both water-miscible materials that permit a greater solubility of the drug. Being the salt of a strong acid and a weak base (pKa 4.5), the final pH is low, approximately 3.0. Upon injection, the buffer capacity of both the tissue and the blood perfusing it gradually restores the pH at the injection site to 7.4. This rise in pH and the absorption of the injected water and water-miscible materials cause chlordiazepoxide base to precipitate out of solution. As movement and hence spreading is minimal, a large mass of drug is deposited around the injection site. The rate of absorption now becomes limited by dissolution of the precipitated drug. However, the small surface area, low solubility, limited perfusion, and minimal stirring tend to keep the rate of dissolution down. The result is protracted absorption over many hours or even days. In contrast, absorption following oral administration is relatively rapid. For reasons already discussed, a greater degree of agitation, a larger volume of fluid at the site, and a higher rate of blood flow to the gastrointestinal tract promote more rapid dissolution and absorption following ingestion of chlordiazepoxide hydrochloride. Another example is diazepam, a drug that is sparingly soluble and slowly absorbed when injected intramuscularly. This essentially neutral drug is kept in solution with the aid of propylene glycol. Precipitation at the injection site occurs with dilution and absorption of this water-miscible solvent.

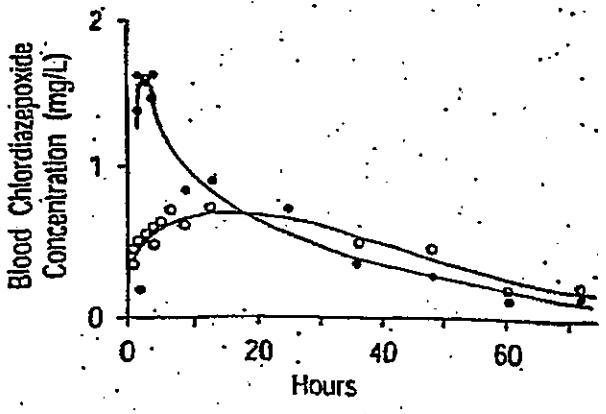

Fig. 9–9. A delayed and lower peak blood concentration of chlordiazepoxide, when given intramuscularly (○—○), as compared to when given orally (●—●), indicates slower absorption from the intramuscular site than from the oral site. On both occasions 50 mg of chlordiazepoxide hydrochloride were administered (1 mg/L = 3.3 μM). (Redrawn from Greenblatt, D.J., Shader, R.I., and Koch-Weser, J.: Slow absorption of intramuscular chlordiazepoxide. N. Engl. J. Med. 291:1116–1118, 1974. Reprinted by permission.)

STUDY PROBLEMS

(Answers to Study Problems are in Appendix II.)

1. List at least three reasons for reduced oral bioavailability of a drug.
2. Indicate the accuracy of the following statements:
   a. When administered orally in solution, gastric emptying rate-limits the absorption of small lipophilic drugs.
   b. For rapidly dissolving products of a drug, differences in rates of dissolution markedly affect the plasma concentration-time profile, when intestinal permeability is the rate-limiting step.
   c. Polar drugs are primarily absorbed from the small intestine via the transcellular route.
   d. A substantial fraction of bioavailable drug enters the systemic circulation via the lymphatic route for large (M.W. greater than 100,000 g/mole) protein drugs administered intramuscularly.
   e. Large nondisintegrating controlled-release dosage forms commonly remain in the stomach for 6 hr when taken just after a heavy meal.
3. List six drugs for which oral bioavailability is low due to a substantial first-pass hepatic loss.
4. List four factors that can influence the rate of dissolution of a drug from a solid dosage form.
5. Comment on the statement: Drugs administered in solution are more slowly absorbed from muscle (i.m. administration) than from the small intestine (oral administration).
6. Listed in Table 9–5 are four drugs together with some of their physical properties.

Table 9–5.

PROPERTY OR CHARACTERISTIC	DRUG A	DRUG B	DRUG C	DRUG D
Molecular weight (g/mole)	327	273	315	378
pKa	8.4 (Acid)	7.8 (Amine)	Neutral	Quaternary ammonium compound
Polarity of unionized form	Nonpolar	Nonpolar	Polar	—
Solubility of unionized form (mg/L)	1.3	150	—	—

Given that the conventional single dose of both Drug A and Drug B is 100 mg and that both drugs are stable in the gastrointestinal fluids, circle the most appropriate drug, word, or phrase (in italics) that completes the following statements.

a. The sodium salt of Drug A dissolves *much faster, much slower, at essentially the same rate,* in a solution of pH 3.0 than (as) does the free acid in a solution of pH 8.0. (Other factors, such as surface area and stirring, are the same.)
b. The hydrochloride salt of Drug B should dissolve *much faster, much slower, at essentially the same rate,* in the stomach of a patient with achlorhydria (no gastric acid secretion) than (as) in a patient with normal gastric function.
c. Drug A is poorly absorbed when taken orally as the free acid with 100 mL of water. The bioavailability of this drug should be significantly increased by taking the drug *with 200 mL of water, in divided doses during the day, on an empty stomach.*
d. Absorption problems are likely to be greater with Drug *A, B,* when administered intramuscularly as an aqueous solution of the *sodium, hydrochloride* salt.

7. In Table 9–6 below are listed the *AUC* values of ciprofloxacin, a drug with a broad antimicrobial activity, following its delivery (180 mg) in solution to various regions of

the gastrointestinal tract. Ciprofloxacin appears to be stable in all parts of the gastrointestinal tract.

Table 9-6. *AUC* Values of Ciprofloxacin after Delivery of 180 mg to Various Regions of the Gastrointestinal Tract[a]

REGION:	STOMACH	JEJUNUM	ILEUM	ASCENDING COLON	DESCENDING COLON
AUC [mg·L/hr]	1.48	0.38	0.24	0.08	0.05

[a]Abstracted from Homer, S., Fuhr, U., Beermann, D., and Staib, A.H.: Ciprofloxacin absorption in different regions of the human gastrointestinal tract investigation with the Hicapsule. Br. J. Clin. Pharmacol., 30:35–39, 1990.

a. From which site of the gastrointestinal tract, stomach, small intestine, or large intestine is the majority of ciprofloxacin likely to be absorbed following oral administration of the drug?
b. Based on the difference in *AUC* values following delivery into the stomach and jejunum, suggest a possible primary site of absorption of ciprofloxacin.
c. For drugs that exhibit absorption patterns similar to that of ciprofloxacin, comment on the chances of successfully achieving a constant systemic input for up to 12 hr following administration of an oral drug-delivery system.

EXHIBIT 24

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 06-222 (JJF)

ANSWERING DECLARATION OF JAMES W. MCGINITY, PH.D.

I, James W. McGinity, Ph.D., declare as follows:

1. I have been retained by Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P. to testify on behalf of Plaintiff Wyeth in this litigation as an expert in the fields of the development and evaluation of pharmaceutical dosage forms. My qualifications as an expert in these areas, as well as in other areas, are set forth fully in my Declaration of May 4, 2007, which was attached as Exhibit 4 to the Declaration of Karen Jacobs Loudon which accompanied Wyeth's Opening Markman Brief of May 8, 2007.

2. I submit this Answering Declaration in response to statements made by Impax in its Opening Markman Brief of May 8, 2007 and, in particular, to statements made in the May 8, 2007 Declaration of Dr. Arthur H. Kibbe, Ph.D. submitted in support of Impax's Opening Markman Brief.

3. I agree with the definition of a person having ordinary skill in the art as stated in paragraph 8 of Dr. Kibbe's May 8, 2007 Declaration, and my May 4, 2007 Declaration as well as this Declaration were made with that definition in mind.

Dr. Kibbe Is Incorrect That The Extended Release Formulations Of The Method Claims At Issue Require "Mandatory" Ingredients

4. I have read the May 8, 2007 Declaration of Dr. Kibbe and, for all of the reasons stated in my Declaration of May 4, 2007, I disagree with his conclusions regarding the meaning of the term "extended release formulation."

5. In particular, at paragraph 14 of his May 8th Declaration, Dr. Kibbe states that because Wyeth's patents disclose that hydroxypropylmethylcellulose ("HPMC") is an optional inactive ingredient in an embodiment of the disclosed extended release formulations, that the remaining inactive ingredients must therefore be "mandatory" for the claimed extended release formulations. I disagree with Dr. Kibbe's conclusion for a number of reasons.

6. First, as noted in my Declaration of May 4, 2007 at paragraph 8, at the time of the invention, those skilled in the art of pharmaceutical formulation recognized that the ordinary meaning of the term "extended release formulation" was a formulation that releases the active ingredient at a slower rate than the immediate release formulation such that the dosing frequency is reduced as compared to the immediate release formulation containing the same active ingredient. As I noted in my Declaration, this ordinary meaning is supported by numerous sources, including definitions in widely used pharmaceutical textbooks and dictionaries, through my personal experiences, and by the testimony of Impax's own witnesses. In short, those of ordinary skill in the art recognize the term "extended release formulation" as not constrained by any specific inactive ingredients.

7. Second, this ordinary meaning of the term "extended release formulation" is entirely consistent with the use of the term in Wyeth's patents. As Dr. Kibbe

recognized in paragraph 15 of his May 8, 2007 Declaration, the patents make clear that conventional hydrogel tablets are excluded from the claimed inventions. Dr. Kibbe ignores, however, the entire discussion of the use aspect of the invention as well as the fact that, as set forth in my May 4th Declaration at paragraph 30, the independent method claims at issue do not recite *any* inactive ingredients for the claimed extended release formulation. Instead, the claims are broadly directed to methods for treating patients with disorders that are responsive to venlafaxine hydrochloride by administering once-a-day an extended release formulation of venlafaxine hydrochloride that provides, among other things, therapeutic blood plasma levels of the drug over 24 hours, and that results in either peak blood plasma level of venlafaxine within a specified time period, or peak blood plasma levels of venlafaxine within specified concentrations. Further, the fact that some of the dependent method claims recite specific inactive ingredients, such as claim 3 of the '120 patent, strongly suggests that the independent method claims should be read to not include such specific ingredients.

8. As I also noted in my May 4th Declaration, one of ordinary skill in the art would recognize that Wyeth's patents disclose a dissolution profile in Table 1 against which other extended release formulations could be screened -- precisely as Impax did in developing its own extended release venlafaxine hydrochloride formulation. In addition, the specification's statements that the "encapsulated formulations of this invention may be produced . . . by techniques understood in the art" and "[t]he following examples are presented to illustrate applicant's solution to the problem ..." indicates that the invention should not be limited to the specific embodiments of Examples 1-7.

9. As a result, Dr. Kibbe's reliance on an isolated portion of the patent specification that describes one embodiment of an extended release formulation as optionally containing HPMC does not support Dr. Kibbe's conclusion that all other disclosed ingredients therefore must be mandatory for all of the claimed extended release formulations.

Impax's Method of Coating Sugar Spheres Is Recognized In The Art Of Extended Release Formulations To Be Equivalent to Extrusion/Spheronization

10. I note that Impax argues that it "has achieved similar *in vivo* blood concentrations (and the corresponding therapeutic anti-depressant effects in the human body) using a different process and set of ingredients nowhere suggested in the patents." [Impax Opening Claim Construction Brief at 6]. However, based on my review of Wyeth's patents, Impax's formulation, and statements made by Impax in Impax's Opening Claim Construction Brief and Dr. Kibbe in his supporting Declaration, it is my opinion that Impax concedes that its "process and set of ingredients" are known interchangeable equivalents to the specific embodiments of extended release formulations disclosed and claimed in the patents.

11. More particularly, at paragraph 32 of his May 8th Declaration, Dr. Kibbe states that "[a]nother method of creating spheroids which was known in the art at the time the patents were filed is the use of coated nonpareil seeds which are simply small beads of sugar." According to Dr. Kibbe, "[t]his is the process used by Impax to manufacture its venlafaxine spheroids."

12. Persons of ordinary skill in the art recognized at the time of Wyeth's invention that the method of coating small beads of sugar with a drug-containing polymeric coating to form a core (as Impax admittedly does) is equivalent to the method of forming a core by extrusion and spheronization using microcrystalline cellulose (as exemplified in the Wyeth patents). Specifically, *Remington's*, the well-known textbook on pharmaceutical science, taught at the time of Wyeth's invention that the coating of sugar spheres with drug-containing polymeric coating was a well-known alternative to extrusion/spheronization processes using microcrystalline cellulose. [Ex. A, *Remington: The Science and Practice of Pharmacy* (19th Ed., 1995) at 1627].

13. Dr. Kibbe correctly concedes in paragraph 19 of his Declaration that techniques for making uncoated drug-containing spheroids, in addition to

extrusion/spheronization, were known and understood by those skilled in the art in 1996. As a result, those skilled in the art need no direction from Wyeth's patents on how to apply these techniques to prepare such uncoated venlafaxine-containing spheroids. Further, they would recognize that Table 1 of Wyeth's patent would be an extremely helpful bench test for screening extended release venlafaxine hydrochloride formulations prepared using these alternative techniques. Those extended release formulations that met the *in vitro* dissolution profile set forth in Table 1 would then advance to the more expensive and time-consuming *in vivo* human testing.

Dr. Kibbe's Conclusion That Wyeth's Patents Teach PVP Is Not An Acceptable Binder For Extrusion Processes Is Incorrect

14. At paragraph 17 of his Declaration, Dr. Kibbe states that the "patent specification indicates that the inventors' attempts to develop formulations with different binders such as polyvinylpyrrolidone failed." From my reading of the patents, Dr. Kibbe's conclusion does not accurately describe their disclosure.

15. REDACTED

16. Further, contrary to Dr. Kibbe's Declaration, Wyeth's patents do not convey that all attempts to develop formulations with different binders such as PVP failed. ['171 patent, col. 5, lines 1-13]. Instead, the patents note that "heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids." Moreover, the patents later explain that the use of the larger scale Hutt and Nica extruders alleviated the difficulty previously experienced, thus indicating that any "difficulty" was equipment specific. ['171 patent. col. 6, lines 6-11].

17.

REDACTED

18. Based on the above, Dr. Kibbe's characterization of the inventors' formulations containing PVP as "failed" is incorrect.

Impax's Contention That Only Microcrystalline Cellulose Can Be Used In An Extrusion/Spheronization Process Is Not Supported By The Evidence

19. I strongly disagree with Impax's statement at pages 6-7 of its Opening Claim Construction Brief that "a 1984 study showed that the extrusion and spheronization process is impossible using any common pharmaceutical excipient other than MCC."

20. As an initial matter, the relevant time period for determining what was known to those skilled in the art was not 1984 as suggested by Impax, but rather in 1996, the effective filing date of Wyeth's patents.

21. Further, I have reviewed the 1984 study [Ex. C, R. O'Connor et al., *Processing and Evaluation of Spheres Prepared from Commercially Available Excipients*, Am. J. of Pharmacy, July-September 1984], relied upon by Impax. The investigation only worked with four single excipients other than microcrystalline cellulose compounds: (1) dibasic calcium phosphate dihydrate; (2) lactose monohydrate; (3) starch; and (4) pregelatinized starch. In addition, water was the only granulating fluid considered in this study. The 1984 study in no way surveys all possible materials that could be used in an extrusion/spheronization process.

22. I am aware of at least two other articles that used different materials than those investigated in the 1984 study, and report that an extrusion-spheronization processes was successful without the use of microcrystalline cellulose. For example, in A. Basit et al., *Formulation of Ranitidine Pellets by Extrusion-Spheronization with Little or No Microcrystalline Cellulose*, Pharmaceutical Development and Technology, Vol. 4, No. 4, (1999) 499-505, [Ex. D], the authors successfully extruded and spheronized

ranitidine hydrochloride using a mixture of barium sulfate, glyceryl monostearate, and water. Similarly, in C. Liew et al., *Functionality of Cross-Linked Polyvinylpyrrolidone as a Spheronization Aid: A Promising Alternative to Microcrystalline Cellulose*, Pharmaceutical Research, Vol. 22, No. 8 (Aug. 2005) 1387-1388, [Ex. E], the authors studied "cross-linked polyvinylpyrrolidone (crospovidone) as a spheronization aid and a promising alternative to microcrystalline cellulose." Crospovidone pellets were found to be of equivalent quality to those prepared with microcrystalline cellulose. The conclusion of the study was that crospovidone can be successfully employed as a spheronization aid.

23. I similarly disagree with paragraphs 16-18 of Dr. Kibbe's Declaration where he appears to equate statements in Wyeth's patents regarding heat buildup in a specific type of extruder with "failed experiments" on any extended release formulation other than those containing microcrystalline cellulose. Specifically, Dr. Kibbe relies on a portion of the specification that states:

> Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such a polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

['171 Patent, col. 5, lines 1-13]. Notably, nothing in this paragraph states that use of different excipients were failures as Dr. Kibbe suggests. Rather, the paragraph states that "heat buildup occurred which dried out the extrudate so much that it was *difficult* to convert the cylinders into spheroids" -- not that the extrudate could not be converted

into spheroids. I therefore disagree with Dr. Kibbe's conclusion that equates difficulty in processing extrudate from one specific type of extruder with failure of any extended release formulation that does not contain microcrystalline cellulose.

24. Further, the portion of the specification referred to in paragraph 17 of Dr. Kibbe's Declaration does not state that all materials tested by the inventors in an extrusion/spheronization process other than microcrystalline cellulose and HPMC are failed experiments.

REDACTED

Moreover, the cited paragraph makes clear that the heat build-up problem occurred in only one type of extruder, an Alexanderwerk extruder. In fact, Wyeth's patents describe the use of alternative, larger scale extruders, such as the Hutt and Nica extruders, where heat build-up was not such a problem.

Unasserted Product Claims

25. I disagree with Dr. Kibbe's conclusions in paragraph 25 and 26. One skilled in the art reading the Wyeth patents would note that significant differences between the independent formulation claims and the independent method claims. Since the independent formulation claims recite specific inactive ingredients, and the independent method claims do not, one of ordinary skill in the art would logically conclude that the method claims are not restricted to the use of any specific set of inactive ingredients.

26. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 24th day of May 2007, at Austin, Texas.

James W. McGinity, Ph.D.

EXHIBIT A

Remington: The Science and Practice of Pharmacy

Nineteenth Edition

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cium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol and microcrystalline cellulose. These commercially available direct-compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids. Dicalcium phosphate dihydrate (Di-Tab, *Stauffer*) in its unmilled form has good flow properties and compressibility. It is a white crystalline agglomerate insoluble in water and alcohol. The chemical is odorless, tasteless and nonhygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is Di-Pac (*Amstar*) prepared by the cocrystallization of 97% sucrose and 3% dextrins. Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow and its use is limited to tablet formulations prepared by the wet granulation method. Both anhydrous lactose and spray-dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets due to its pleasant taste and mouth-feel resulting from its negative heat of solution. In its granular form (*ICI Americas*) it has good flow and compressible qualities. It has a low moisture content and is not hygroscopic.

The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, *FMC*). This nonfibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades which range in average particle size from 20 to 100 μm. It is water insoluble but the material has the ability to draw fluid into a tablet by capillary action; it swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus requiring a lower level of lubricant as compared to other excipients.

Forced-flow feeders are mechanical devices available from pharmaceutical equipment manufacturers designed to deaerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained. See Fig 14.

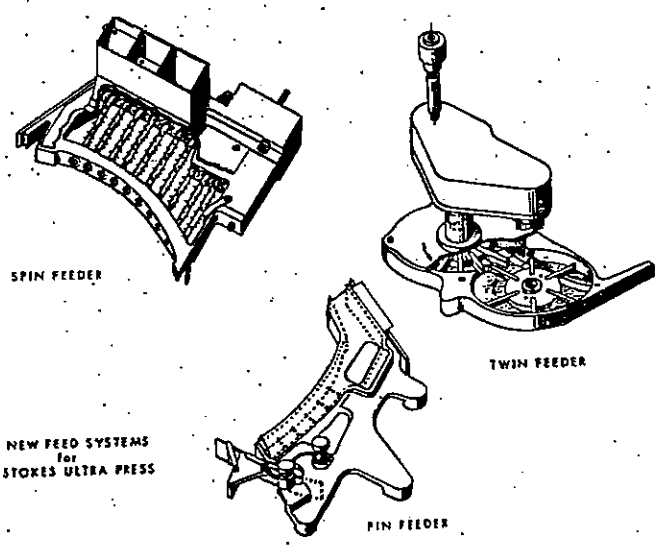

Fig 14. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes/Pennwalt).

Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as "forgiving" as were the older wet-granulated products. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression also is stimulating basic research on the flowability of powders with and without the presence of additives. Direct compression formulas are included in the formula section found on page 1636.

Related Granulation Processes

Spheronization—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment such as the Marumerizer (*Luwa*) and the CF-Granulator (*Vector*) is commercially available. A wet granulation containing the drug substance, diluent (if required) and binder, is passed first through an extruding machine to form rod-shaped cylindrical segments ranging in diameter from 0.5 to 12 mm. The segment diameter and the size of the final spherical particle depend on the extruder screen size. After extrusion the segments are placed into the Marumerizer where they are shaped into spheres by centrifugal and frictional forces on a rotating plate (see Fig 15). The pellets then are dried by conventional methods, mixed with suitable lubricants and compressed into tablets, or used as capsule-fill material. Microcrystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized.[35–38] The advantages of the process include the production of granules, regular in shape, size and surface characteristics; low friability resulting in fewer fines and dust; and the ability to regulate the size of the spheres within a narrow particle-size distribution.

Spheres also can be produced by fluid-bed granulation techniques and by other specialized equipment such as the CF-Granulator (*Vector*). These processes, however, must begin with crystals or nonpareil seeds followed by buildup. Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

Spray-Drying—A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying. The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed liquid may be a solution, slurry, emulsion, gel or paste, provided it is pumpable and capable of being atomized. As shown in Fig 16, the feed is sprayed into a current of warm filtered air. The air supplies the heat for

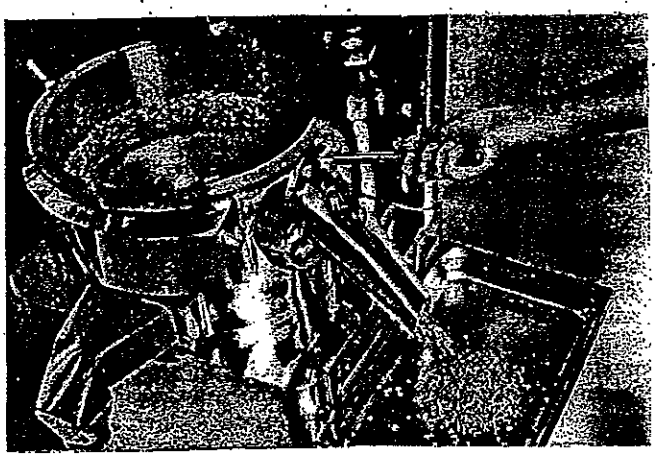

Fig 15. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

EXHIBIT B

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EXHIBIT C

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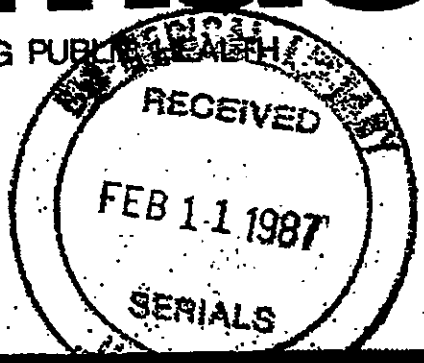

ARTICLES

Spheronization I:

Processing and Evaluation of Spheres Prepared from Commercially Available Excipients

Robert E. O'Connor, Jurij Holinej, and Joseph B. Schwartz

The processing characteristics of materials used to manufacture spheres was studied using commercially available equipment. The materials include several common diluents and binders evaluated in single-component systems. Results demonstrate that under similar processing conditions the quality of the spheres produced depends on the starting material. Physical testing includes particle size analysis, density, and friability. Preliminary dissolution results on spheres containing active ingredients indicate that the release pattern varies with the matrix material and with the drug concentration.

Spheres for pharmaceutical uses are of interest for both conventional dosage forms and controlled release delivery systems. The typical application of spheres is as capsule fill material in controlled-release formulations; however, the spheres can also be used in tableting. In this study emphasis has been directed toward the materials used to prepare larger spheres using an extruder (Model EXDS-60, LUWA Corp., Charlotte, NC) and spheronizer (Model Q-230, LUWA Corp.). (See Fig. 1.) The spheronization process using the extruder and spheronizer has been described[1,2] and utilized[3–6] by other researchers. In this paper, the processing parameters are held constant

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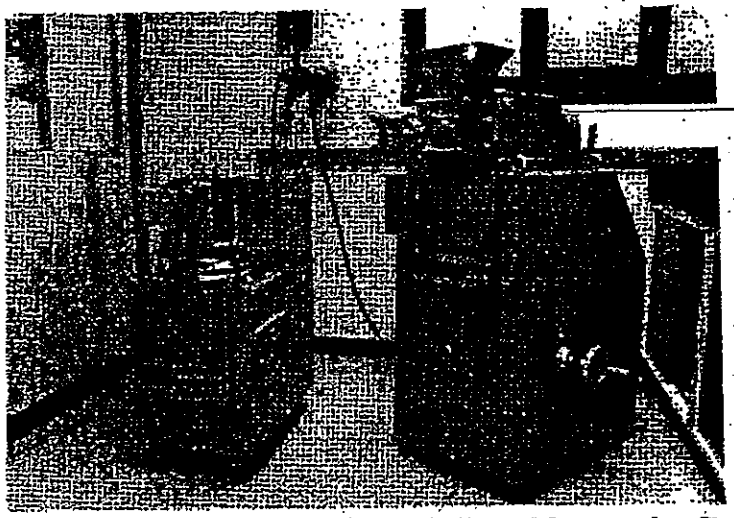

Fig. 1. Extruder (right) and spheronizer (Marumerizer®).

to study material behavior rather than varying the parameters with respect to a given formulation. The materials are studied in single component systems to determine their applicability to the spheronization process. This rudimentary approach has been used previously in a limited study by Miyake, *et al.*,[7] in which three excipients were evaluated.

EXPERIMENTAL

Materials

The excipients evaluted included: Dibasic Calcium Phosphate Dihydrate USP (Monsanto, St. Louis, MO), Lactose Monohydrate USP (Ruger Chemical Co., Irvington, NJ), Microcrystalline Cellulose NF (Avicel PH types, FMC Corp., Philadelphia, PA), Microcystalline Cellulose and Carboxymethylcellulose Sodium NF (Avicel RC/CL types, FMC Corp.) Starch USP (Ruger Chemical Co.), Pregelatinized Starch NF (Starch 1500, Colorcon, Inc., West Point, PA).

The active ingredient used for the preliminary dissolution work was Theophylline Anhydrous USP (FMC Corp.).

Method

The method is outlined in Fig. 2 as a processing flow chart. The materials were granulated in a planetary mixer (Model A-200T, Hobart Corp., Hobart, NY). Batch size was held constant at 1.0 kg of dry solid. Purified water USP was added to the mixing powders to achieve the proper consistency for extrusion. The wetted mass was passed through the extruder which was operated at 50 rpm and was fitted with 1.5-mm screens. The extrudate was then processed in the spheronizer (see Fig. 3) immediately following extrusion. The spheronizer was operated at 1000 rpm and was fitted with a 2-mm scored friction plate. Product was collected at both 1- and 2-min residence times. The spheronized product was dried on paper-lined trays either by air or in a hot air oven (Stokes Model 38C, Pennwalt Corp., Warminster, PA).

Physical Testing

Loss on Drying—The Loss on

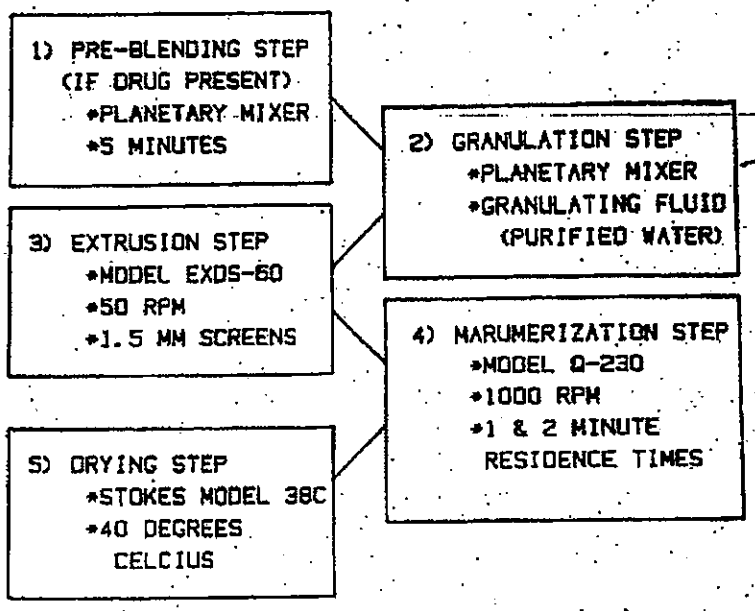

Fig. 2. Processing flow chart for spheronization.

Drying (LOD) was determined on a moisture balance (Cenco, Central Scientific, Chicago, IL) at a heat setting of 70 with a 15-min testing time. The product was dried until it had an LOD equal to or less than that of the starting material.

Sieve Analysis—A 100-g sample was placed on a nest of tared US standard sieves, which were then placed on a vibrating sieve shaker (Cenco-Meinzer, Central Scientific, Chicago, IL) for 5 min.

Particle Size—The geometric

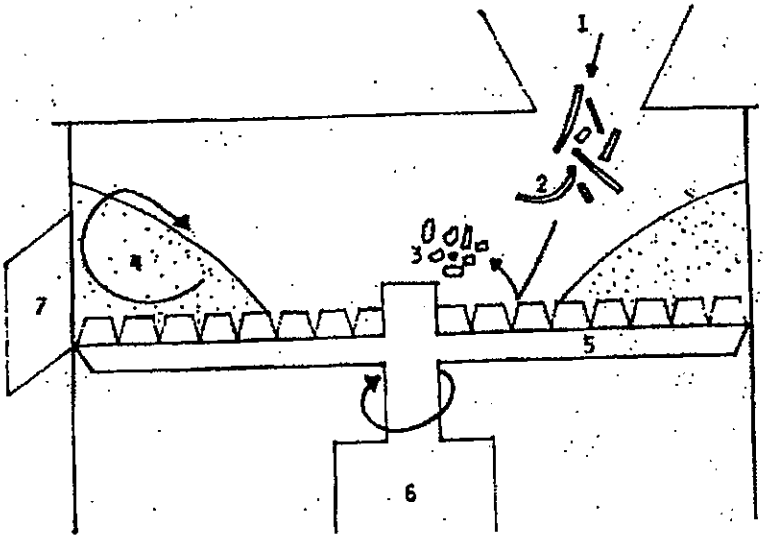

Fig. 3. Schematic of spheronizer (Marumerizer®). Key: 1—Feed inlet; 2—Extrudate; 3—Breakage into short rods; 4—Rope-shaped bed; 5—Friction plate; 6—Drive unit; 7—Product outlet).

mean diameter (d'g) was determined graphically on log-probability graph paper as discussed by Martin.[8] The cummulative percent undersize and average particle size were determined from sieve analysis data and were plotted on the ordinate and abscissa, respectively.

Friability Test—A 10-g sample of a specified mesh cut (usually 16/20 mesh cut retained from sieve analysis) was placed in a friabilator (Erweka, Inc., Fairfield, CT) fitted with an abrasion wheel with 200 glass beads (4 mm) and rotated for 10 min. This test is a modification of that used previously by Malinowski.[9]

Density Determination—The bulk and tapped density were determined using a 25-g sample. The volume occupied by the product was recorded at 0, 3, 10, 25, 50, and 100 taps or until no change in volume occurred.

Dissolution Testing—Dissolution testing was performed in 900 ml of distilled water at 37°C using USP Method I over a 4-hr time period with a basket rotational speed of 50 rpm. The samples were analyzed by UV spectroscopy at 272 nm.

Results and Discussion

The manufacturing results are presented as a processing summary in Table 1. The Avicel PH, RC, and CL types processed satisfactorily, but Dibasic Calcium Phosphate Dihydrate USP, Lactose Monohydrate USP, Starch USP, and Pregelatinized Starch NF were not amenable to the spheronization process as single components. In general, the Avicel PH types produced superior spheres under these simple processing conditions. For Avicel RC types, the balance between cohesion and plasticity has been found to favor cohesion which results in the formation of a mixture of spheres and short rods. Avicel CL-611 appears to lack the necessary plastic properties but was very cohesive and formed longer rods in the spheronizer.

Representative results of physical testing for Avicel PH-101 spheres are reported in Table 2. (*Note:* The interested reader is referred to the authors for complete data sets.)

The sieve analysis data were further analyzed to determine the particle size distribution. After 1 min in the spheronizer, it was found that 90.11–98.93% of each batch passed through 12 mesh sieve and was retained on a 30 mesh sieve (12/30 mesh cut). After 2 min, the range was determined to be 93.62–98.55% of

Table 1—Processing Summary for Single Component Systems

Excipient	Operations Completed			Product Description
	Granulation	Extrusion	Spheronization	
Avicel PH types	yes	yes	yes	spheres
Avicel RC types	yes	yes	yes	spheres and short rods
Avicel CL types	yes[a]	yes	yes	longer rods
Calcium phosphate	no	—	—	none
Lactose	yes	yes	no	none
Starch	no	—	—	none
Starch 1500	yes	no[b]	—	none

[a] Processed at a lower liquid level.
[b] Extrudate formed continuous, nonsegmented strands.

Table 2—Representative Results of Physical Testing for Avicel PH-101 Spheres[a]

Test Identification		Spheronizer Residence Time 1 min	2 min
Sieve Analysis	*% Retained on Screen*		
	8	0.17	0.36
	12	2.53	5.71
	16	26.53	37.05
	20	52.60	47.06
	30	15.90	9.51
	40	2.16	0.28
	Pan	0.11	0.03
Geometric mean diameter (d'g in μm)		860	1010
Density (g/ml)		0.76[b]	0.78[b]
Friability (% weight loss)		5.46	3.07

[a] The interested reader is referred to the authors for complete data sets.
[b] This value represents both bulk and tapped density, since the cascade volume was found to represent closest packing arrangement.

the product in a 12/30 mesh cut. The slight increase in the amount of 12/30 mesh cut spheres does not appear worth the effort of doubling the residence time. These data represent a narrow particle size distribution relative to those reported by Reynolds for a typical wet granulation.[2] Reynolds' sieve analysis data for spheronized product correlated with the values found in this study.

Particle Size

The geometric mean diameter (d'g) was determined from the sieve analysis data and ranged from 720–1020 μm. From the physical appearance of the product prepared from the Avicel RC and CL types (see Table 1), it is apparent that some degree of vertical orientation must have occurred during sieve analysis. The known limitations of size classification by sieving were experienced in this study. However, much of the inherent error associated with sieving is eliminated when testing spherical products (e.g., Avicel PH types).

Friability

In this work, the friability generally decreased with increasing spheronizer process time. Overall, the spheres produced appear very hard and seem likely to withstand any subsequent rough handling in packaging or, possibly, in coating operations.

Density

The density values are listed in Table 3 and include spheronized product and corresponding untreated powders.

An interesting phenomenon occurred in determining the density of the spheres. The cascade volume for bulk density calculation was found to represent "closest packing" and tapping appeared to disturb this packing arrangement resulting in greater volumes and, subsequently, lower densities. Since tapping resulted in lower densities, the reported values for the spheronized product represent both bulk and tapped densities.

The bulk density increased significantly for all excipients as a result of

Table 3—Product and Powder Density

Excipient	Product Spheronizer Residence Time 1 min	Product Spheronizer Residence Time 2 min	Untreated Powder Bulk	Untreated Powder Tapped
Avicel PH-101	0.76	0.78	0.28	0.40
Avicel PH-102	0.76	0.81	0.30	0.40
Avicel PH-103	0.81	0.81	0.32	0.44
Avicel PH-105	0.81	0.81	0.24	0.36
Avicel RC-501	0.83	0.86	0.64	0.88
Avicel RC-581	0.83	0.83	0.66	0.92
Avicel RC-591	0.81	0.86	0.68	0.86
Avicel CL-611	0.86	0.80	0.64	0.83

spheronization. The tapped density increased for the PH types but remained approximately the same for the RC and CL types. Overall, the effect of processing on the increase in density depended on the starting material. The density of the spheronized products was greater than the values found in the literature for conventional granulations produced by the wet method.[10,11]

Conclusion

Based on the data and discussions presented, it can be concluded that the extruder/spheronizer combination is capable of producing spheres from certain simple systems using only purified water as the granulating liquid. Identical treatment for all excipients does not yield identical product, in fact, not all materials will process as single entities. Relative to conventional wet granulations, spheronized granulations are more dense, more spherical in shape, and exhibit a narrow particle size distribution.

Preliminary Dissolution Results

The preliminary dissolution results are presented in Fig. 4 for 10% the-

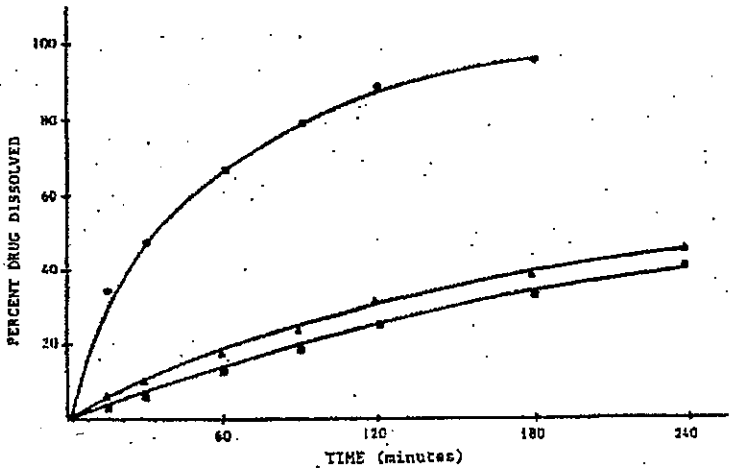

Fig. 4. Dissolution profiles for products containing 10% theophylline in different Avicel MCC types (Key: ● Avicel PH-101; ▲ Avicel RC-581; ■ Avicel CL-611).

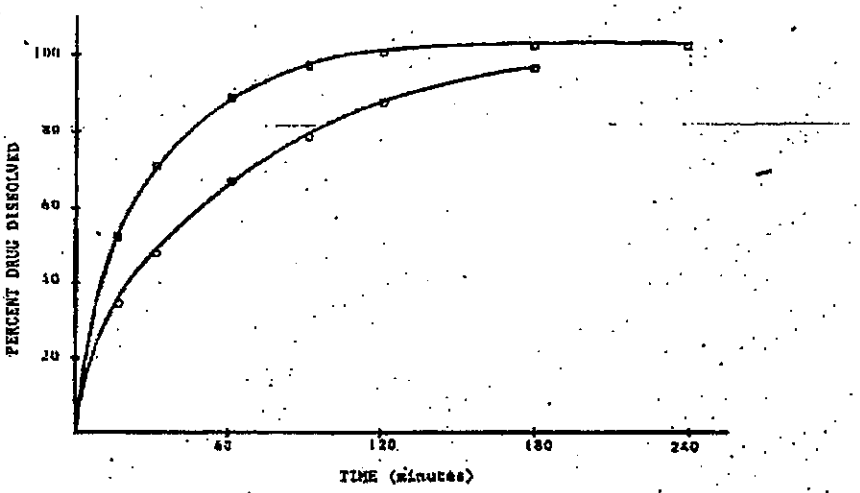

Fig. 5. Dissolution profiles for products containing different concentrations of theophylline in Avicel PH-101 (Key: O 10%; □ 50%).

ophylline in Avicel PH-101, Avicel RC-581 or Avicel CL-611 and in Fig. 5 for 10% or 50% theophylline in Avicel PH-101.

The preliminary dissolution results for the 10% theophylline products indicate that the release pattern appears to depend on the excipient used for the matrix. A comparison of release profiles for 10% and 50% theophylline in Avicel PH-101 suggest that drug release also may depend on drug concentration.

In general, these simple binary mixtures exhibit varying degrees of delayed release by the test method selected and warrant further study of binary drug-diluent mixtures.

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EXHIBIT D

Pharmaceutical Development and Technology, 4(4), 499–505 (1999)

RESEARCH ARTICLE

Formulation of Ranitidine Pellets by Extrusion–Spheronization with Little or No Microcrystalline Cellulose

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ABSTRACT

The present study was concerned with the feasibility of formulating ranitidine into pellets with a range of alternative excipients in place of microcrystalline cellulose (MCC). Eight ranitidine formulations employing two or more of the excipients lactose, barium sulfate, glyceryl monostearate, and MCC were processed by extrusion–spheronization, and characterized according to a series of physico-mechanical and dissolution criteria. Formulations containing lactose produced unsatisfactory pellets of wide size distribution and irregular shape, whereas formulations incorporating barium sulfate and glyceryl monostearate with or without MCC resulted in relatively spherical pellets of narrow size distribution and good mechanical properties. Ranitidine release was found to be rapid and virtually complete within 15 min, regardless of the pellet formulation. A direct relationship was observed between the concentration of MCC in the formulation and the properties of the pellets. In general, the higher the concentration of MCC, the rounder, stronger, and less friable the pellets. However, even pellets without MCC were also successfully prepared with a superior size distribution and shape over those with MCC. Overall, these results confirm that ranitidine can be formulated into pellet dosage forms with little or no MCC by the extrusion–spheronization process.

KEY WORDS: Barium sulfate; Extrusion–spheronization; Glyceryl monostearate; Instability; Microcrystalline cellulose; Pellet; Ranitidine.

INTRODUCTION

Pellets, as oral dosage forms, offer several distinct advantages over more conventional single-unit systems. Their small size and divided nature permit ease of handling, coating, and dose adjustment as well as more reproducible gastrointestinal transit and subsequent drug absorption (1).

Although a variety of processes have been used to produce pellets, arguably the best is extrusion followed by spheronization. Basically, the process comprises a series of noncontinuous stages, the first of which involves mix-

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ing the drug and any excipients with a liquid binder, usually water, to form a wet powder mass. This is followed by extrusion of the wet mass through a die to form cylindrical strands of uniform length and diameter. Spheronization follows, in which the strands are chopped into equal lengths before being rounded into pellets of spherical shape. Finally, the wet pellets are collected and dried in either a fluidized bed or tray drier prior to use. As with most processes, however, there is a strong interdependence between the formulation, the equipment, and the processing conditions (2,3).

Successful extrusion–spheronization requires the production of a cohesive wet mass that is able to flow through the die without adhering to the extruder or itself, while retaining a degree of rigidity so that the shape imposed by the die is retained. Furthermore, the extrudate must be brittle enough to break into uniform lengths on the spheronizer plate, yet still be plastic enough to round into spherical pellets (4). However, most drugs do not possess such ideal characteristics, and therefore require the addition of microcrystalline cellulose (MCC) to produce formulations with the necessary rigidity, plasticity, and water absorbing capacity required for extrusion–spheronization (5–7).

The use of MCC may be undesirable, however, in cases where the drug is unstable in its presence. Such instability was found to occur with the highly water-soluble drug, ranitidine, when formulated as a pellet dosage form containing in excess of 60% MCC. The instability involved chemical degradation of the drug by means of a complex three-way interaction between ranitidine, MCC, and the liquid binder, namely water. As a means of overcoming such instability, alcohol could possibly be used instead of water as the liquid binder; however, previous work showed that pellets prepared from alcohol tend to be weak, friable, and irregular in shape (8). In addition, the use of alcohol has its own inherent disadvantage with regard to flammability and toxicity hazards. Reducing or even completely removing the amount of MCC from the formulation is an alternative approach to the problem. However, seemingly few studies have addressed the issue of formulating drugs into pellets with little or no MCC by the process of extrusion–spheronization.

The present study was therefore undertaken to investigate the feasibility of formulating ranitidine into pellets with a range of alternative excipients to MCC.

MATERIALS AND METHODS

Materials

Ranitidine in the form of the hydrochloride salt was certified as 99.9% pure and of 87.82 μm median particle size, 1.29 g/cm³ density, and 0.11% moisture content, (GlaxoWellcome, Ware, U.K.). MCC (Avicel® PH101) of 50.69 μm median particle size, 1.52 g/cm³ density, and 4.03% moisture content (FMC Corp., Philadelphia, PA) was used as the filler. Lactose of 33.54 μm median particle size, 1.52 g/cm³ density, and 5.33% moisture content (Sheffield Products, Norwich, NY); barium sulfate of 10.22 μm median particle size, 4.37 g/cm³ density, and 0.14% moisture content (Sachtleben Chemie GmbH, Duisberg-Homberg, Germany); and glyceryl monostearate of a particle size less than or equivalent to 100 μm, 0.98 g/cm³ density, and 0.20% moisture content (Hüls, Milton Keynes, U.K.) were used as alternative fillers to MCC. The liquid binder was freshly distilled water. A commercial tablet formulation (Zantac®) containing 168 mg ranitidine hydrochloride (≈150 mg ranitidine) was used as a model dosage form for comparison purposes during the dissolution studies (GlaxoWellcome).

Preparation of Pellets

Fifty-gram batches of formulations A–H (Table 1) were dry mixed for 5 min using a pestle and mortar. Sufficient distilled water was added, via a syringe, and mixing continued for a further 10 min to obtain a wet powder mass suitable for extrusion.

Extrusion was undertaken using a ram extruder, the principles and advantages of which were detailed elsewhere (2,4,9), as well as its correlation in terms of performance with a large-scale extruder (10). The wet mass was packed into the barrel of the ram extruder of 2.5 cm internal diameter and 20.3 cm length to which was fitted a die of 1 mm diameter and 4 mm length. A piston was inserted into the barrel to partially consolidate the wet mass. The barrel, die, and piston assembly was mounted on a rigid support and then positioned under the crosshead of a calibrated servo-hydraulic press (model MX50, J.J. Lloyd, Southampton, U.K.). The crosshead was driven at a constant rate of 200 mm/min and the force exerted by the piston was recorded as a function of displacement via a computer.

The products of the extrusion process were processed using a 12-cm-diameter spheronizer (G.B. Caleva Ltd., Sturminster Newton, U.K.) with a cross hatch plate rotating at 1883 rpm for periods of up to 30 min. The pellets formed were collected and dried in a fluidized bed drier (model FDBL 70, P.R.L. Engineering Ltd., Flintshire, U.K.) at 60°C for 15 min prior to further evaluation.

Characterization of Pellets

The resultant pellets were characterized according to the following physico-mechanical and dissolution criteria.

Table I

Composition of Pellet Formulations

Formulation	Ingredients (%)					
	Ranitidine Hydrochloride	Microcrystalline Cellulose	Barium Sulfate	Lactose	Glyceryl Monostearate	Water[a]
A	50	20	30	—	—	9.9
B	50	15	30	—	5	7.8
C	50	10	40	—	—	6.9
D	50	10	—	40	—	4.3
E	50	10	—	30	10	4.6
F	50	10	30	—	10	7.1
G	50	5	30	—	15	5.9
H	50	—	30	—	20	4.8

[a]Water added as a percentage of the total dry weight of each formulation.

Size Distribution

Pellets were screened according to size through a nested set of British standard sieves with a $2^{1/2}$ progression ranging from 0.71 to 2.00 mm in size using a mechanical sieve shaker (Endecott Ltd., London, U.K.) for 10 min. The weight of pellets retained on each sieve was recorded and presented as a cumulative weight percentage oversize curve, from which the median pellet size and interquartile range were obtained for each batch of pellets. However, only pellets within the 1.4- to 1.7-mm size range were used in subsequent characterization tests.

Shape

The sphericity of the pellets was assessed using a previously described image analysis technique (11). Fifty pellets from each batch were placed on a petri dish and positioned under a cold light source for illumination purposes. A zoom lens (model 18-108/2.5, Olympus, Hamburg, Germany) connected to a black and white camera (model CCD-4, Rengo Co. Ltd., Toyohashi, Japan) and an image analyzer (model Solitaire 512, Seescan, Cambridge, U.K.) were used to view the pellets. The image analysis program calculates a two-dimensional shape factor (ϵ_R) and its associated standard deviation, which is dependent on both the eccentricity and surface roughness of the pellets. Theoretically, only a circle can have a shape factor of 1.0. For other shapes, the value is less than 1.0 and can even be negative for very elongated or rough pellets. As a comparison, a completely spherical steel ball bearing was found to have a shape factor of 0.76, and therefore a value of above 0.50 is generally considered satisfactory in terms of pellet sphericity (11).

Strength

The force required to crush individual pellets was determined using a conventional tablet strength tester (model CT40, Engineering Systems, Nottingham, U.K.). The test was performed on 10 pellets from each batch.

Friability

Pellet friability was ascertained using a friabilator (Erweka, Frankfurt, Germany). Approximately 5 g of pellets was accurately weighed and added to the friabilator, which was set to run at 34 rpm for 15 min. At the end of the run, the contents were added to a 1-mm sieve and the pellets remaining on the sieve surface were weighed. The difference in weight before and after the run provides a measure of pellet friability and was calculated as follows:

$$\text{Friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \quad (1)$$

Each batch was assessed in triplicate.

Density and Porosity

The true density of the pellets was measured using an air comparison pycnometer (model 930, Beckman, Fullerton, CA). Each batch was repeated in triplicate, with random 10-g samples taken each time, and the average density was calculated. The porosity was then calculated from the following equation:

$$\text{Porosity} = \left[1 - \frac{\text{pellet density}}{\text{powder density}}\right] \times 100 \quad (2)$$

where pellet density is the average density of the pellets and powder density is the sum of the average densities of the powder components of the pellet formulation.

Residual Moisture Content

The residual moisture remaining within the pellets was determined using a thermogravimetric analyzer (model 2950, TA Instruments, New Castle, DE). The pellets were initially crushed using a pestle and mortar and then sieved through a 250-μm sieve in order to obtain a relatively constant particle size before loading into an aluminum sampling pan (sampling pan kit, Perkin-Elmer, Norwalk, CT). Approximately 5-mg samples were loaded in each case and then crimped with an aluminum lid prior to analysis. Each sample was heated over a temperature range of 30–140°C at the rate of 10°C/min. The gradual percentage weight loss with increasing temperature was recorded for each batch of pellets in triplicate.

Dissolution

The in vitro ranitidine release from the pellets was determined using a method 2 dissolution test apparatus (model PTWS, Pharma Test, Hainburg, Germany) as described in the USP 23. All of the tests were conducted in 900 ml of 0.1 N hydrochloric acid (pH 1.2) maintained at 37.0 ± 0.5°C with a paddle rotation speed of 100 rpm. In each case, 340 mg of pellets (≈168 mg ranitidine hydrochloride ≈ 150 mg ranitidine) was used. Three-milliliter samples were withdrawn at various predetermined time intervals using an automated sampler (model PTFC-1, Pharma Test). The ranitidine concentration in each sample was determined using a UV–VIS spectrophotometer (model 554, Perkin-Elmer, Ueberlingen, Germany) set at a wavelength of 313 nm. The percentage ranitidine released over time was calculated and plotted as an average of six runs using calibration curves consistent with Beer's law. As a comparison, drug release was also determined from a commercial tablet formulation containing 150 mg ranitidine (Zantac) (GlaxoWellcome).

RESULTS AND DISCUSSION

Preparation of Pellets

A series of eight formulations (A–H) were systematically designed (Table 1). The ranitidine content in each formulation was kept constant at 50% and the amount of MCC was restricted to 20% or less. The remainder of each formulation was kept as simple as possible comprising different combinations of the following excipients: lactose, barium sulfate, and glyceryl monostearate. These excipients were chosen as potential alternatives to MCC for a variety of reasons, but primarily on the basis of previous work, which confirmed their beneficial effects when incorporated into formulations destined for extrusion–spheronization (12).

For each formulation, the critical water content necessary to achieve the correct consistency for extrusion–spheronization is shown in Table 1. The total amount of water added in each case was considerably lower than for most formulations, which usually require a ratio of 1.2 parts water to 1 part MCC (13). This apparent anomaly can be related in part to the freely soluble nature of ranitidine, since formulations containing soluble drugs require less water for successful extrusion–spheronization (14). It is worth noting, however, that not all drugs are amenable to this process. For example, there is no known relationship between chemical structure and processability, although it is known that drugs with high water solubility tend to present problems. Ranitidine is potentially a prime example of such a drug, and it is not surprising that with these formulations pellet formation was found to be both difficult and highly dependent on the water content. The problem was further compounded by the limited quantities of MCC in each formulation, because MCC, with its unique properties, is generally considered to be an essential excipient in the extrusion–spheronization process (2,3). On many occasions, overwetting of the powder mass prior to extrusion led to uncontrollable agglomeration of the extrudate during spheronization. On other occasions, however, too dry a powder mass resulted in fragmentation of the pellets during spheronization. Although it is normally possible to vary the water content over a finite range and still produce pellets of an acceptable quality (13,15), such measures were not possible with the formulations at hand. Therefore, the critical water content for each formulation was determined by trial and error, rather than by any scientific means.

As a further consequence of the limited quantities of water and MCC present within each formulation, the steady-state extrusion forces and spheronization times were far in excess of those routinely reported in the literature (Table 2) (4,13,15), presumably due to a lack of sufficient plasticity within the formulations themselves. Formulations containing greater quantities of MCC (A and B) were therefore easier to extrude and spheronize. Nevertheless, pellets were obtained from all eight formulations, albeit with difficulty.

Characterization of Pellets

Formulations containing the water-soluble excipient, lactose (D and E), produced unsatisfactory pellets of ir-

Table 2

Extrusion-Spheronization Process Conditions and Pellet Size and Shape Characteristics

Formulation	Extrusion force (kN)	Spheronization Time (min)	Size Distribution (mm)		Shape Factor ($e_R \pm SD$)
			Median	Interquartile Range	
A	15.2	16	1.61	0.33	0.53 ± 0.05
B	17.2	15	1.61	0.32	0.49 ± 0.10
C	18.4	19	1.50	0.27	0.45 ± 0.11
D	16.3	22	1.47	0.79	0.33 ± 0.17
E	16.1	20	1.61	0.45	0.30 ± 0.19
F	18.2	14	1.63	0.31	0.47 ± 0.06
G	18.7	16	1.59	0.27	0.51 ± 0.03
H	19.2	25	1.59	0.21	0.58 ± 0.06

regular shape and wide size distribution (Table 2), probably because of the inappropriate rheological characteristics of their wet powder masses.

In contrast, incorporation of the water-insoluble excipient, barium sulfate, in place of lactose (A and C), resulted in the formation of a better product. These pellets were more spherical in shape and of a narrow size distribution. In essence, the barium sulfate provides a greater degree of support and structure to the pellet formulations, and to a certain extent counters the high water solubility of ranitidine. Nevertheless, the pellets were slightly larger than expected, with more than 60% of the pellets within the 1.4- to 1.7-mm size range, even though a die of 1 mm diameter was used in the extrusion process. Jaiyeoba and Spring (16) claimed that granule size was influenced by the physical properties of the constituent powders, the proportion of components in the powder mixture, and the type and quantity of binder. On the assumption that the same argument holds true for pellets, the larger than expected pellet size may be related to the properties of ranitidine itself, especially its high solubility within the liquid binder. During the wet massing stage, some of the drug is likely to have dissolved in the water, increasing the volume of the liquid phase. This may lead to overwetting of the system (17), and hence the formation of larger pellets. It would therefore appear that pellet size is a complex and composite function of not only the diameter of the die used, but also the properties of the drug and its associated formulation.

In addition to their satisfactory shape and size, the pellets were fairly strong in nature with little or no friability, as shown in Table 3. Their dissolution release profiles were rapid and virtually complete within 15 min (Fig. 1). Formulations incorporating glyceryl monostearate (B, F, and G) resulted in pellets that were slightly weaker and more friable than others, but of a similar shape and size distribution. The rate of drug release was slightly slower, although not to any appreciable extent, possibly due to the presence of glyceryl monostearate forming a hydrophobic water-retarding barrier within the pellets. Nevertheless, drug release was considerably faster from each pellet formulation than the commercial tablet formulation

Table 3

Pellet Characteristics of Ranitidine Formulations

Formulation	Crushing Force (kg ± SD)	Friability (% ± SD)	Density (g/cm^3 ± SD)	Porosity (%)	Moisture Content (% ± SD)
A	1.16 ± 0.12	0.03 ± 0.01	1.56 ± 0.01	30.97	0.86 ± 0.07
B	1.09 ± 0.11	0.05 ± 0.01	1.53 ± 0.02	31.48	0.64 ± 0.08
C	1.21 ± 0.11	0.15 ± 0.02	1.70 ± 0.02	33.20	0.48 ± 0.05
D	0.88 ± 0.14	0.10 ± 0.01	1.36 ± 0.01	3.20	2.32 ± 0.13
E	0.66 ± 0.10	0.08 ± 0.02	1.26 ± 0.01	6.74	1.96 ± 0.11
F	0.61 ± 0.06	0.11 ± 0.02	1.60 ± 0.02	27.47	0.44 ± 0.05
G	0.37 ± 0.09	0.15 ± 0.01	1.52 ± 0.02	30.24	0.28 ± 0.03
H	0.35 ± 0.07	0.16 ± 0.02	1.44 ± 0.01	33.09	0.22 ± 0.04

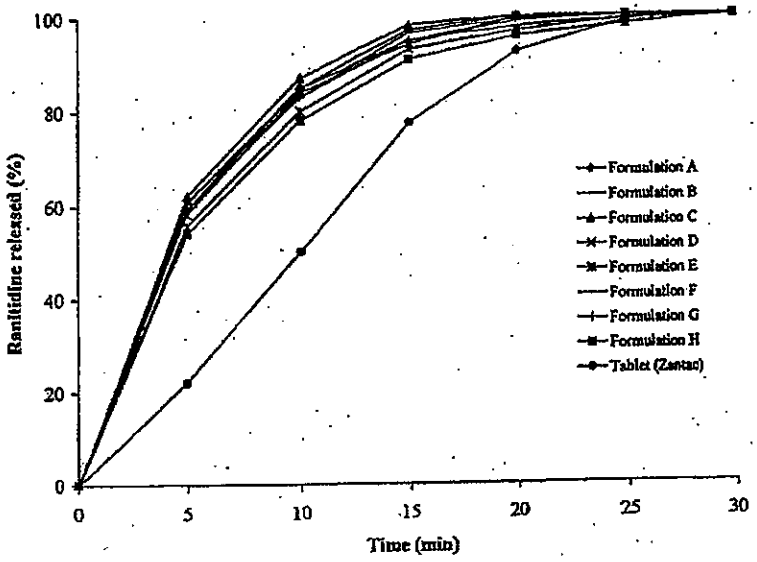

Figure 1. In vitro dissolution profiles comparing ranitidine release from the pellet formulations and the commercial tablet formulation (Zantac).

(Zantac). This is not unduly surprising since the pellets have a greater exposed surface area from which drug release can occur.

The pellets thus far have all had in common the presence of MCC. As expected, a direct relationship was observed between the concentration of MCC in the formulation and the properties of the pellets; in general, the higher the concentration of MCC, the rounder, stronger, and less friable the pellets. However, even pellets without MCC (H) were also successfully prepared with both an improved size distribution and sphericity over those containing MCC. This improved sphericity, although surprising, was consistent with previous work and suggested that glyceryl monostearate was superior to MCC as a rounding agent in the formation of spherical pellets (12).

Relationships were also observed between the true density, porosity, and residual moisture content of the pellets and the ingredients of the formulation. Pellets containing barium sulfate (A, B, C, F, G, and H) were both denser and more porous than those containing lactose (D and E). The greater density was due to the greater inherent density of barium sulfate itself, whereas the increased porosity can be attributed to the higher water content required to produce wet powder masses of the correct consistency. On drying, the water evaporates leaving behind a network of pores within the pellet structure. Such pores have been known to affect the rate of drug release from pellets, but in the present study no appreciable difference in drug release was noted, presumably because of the high water solubility of ranitidine. In terms of residual moisture content, pellets incorporating barium sulfate (A, B, C, F, G, and H) contained less moisture than those incorporating lactose (D and E), by virtue of barium sulfate's lower inherent moisture. Barium sulfate could therefore be used as a suitable alternative to MCC in pellet formulations containing water-sensitive drugs.

If one considers all of the aforementioned test criteria, it is reasonable to surmise that pellets containing lactose display less than ideal physico-mechanical characteristics, whereas those containing barium sulfate and glyceryl monostearate demonstrate sufficient strength and shape required for everyday handling and further processing, such as film coating, if necessary. Although not reported here, these pellets were also found to be chemically stable during short-term stability studies, thereby overcoming the previous instability problems encountered with formulations containing ranitidine and high levels of MCC. Hence, for the purpose at hand, both barium sulfate and glyceryl monostearate were more than satisfactory replacements for MCC.

This study provides a guide to the formulation of ranitidine pellets with little or no MCC. It should be appreciated, however, that these results may not be universally applicable to all drugs, especially those with properties vastly different from those of ranitidine, such as solubil-

ity, particle size, size distribution, and shape, or those drugs that require a loading higher than the 50% reported here. In such cases, the findings of this study can still be used as a starting point, although further work may be necessary to achieve a satisfactory formulation

CONCLUSIONS

The present study demonstrated the feasibility of formulating ranitidine into pellet dosage forms with barium sulfate and glyceryl monostearate in place of MCC. Such pellets exhibit the necessary physical and mechanical characteristics required of oral dosage forms and for further pharmaceutical processing such as film coating. Overall, these findings have important implications in cases where drug–MCC incompatibilities arise, necessitating a reduction in concentration or complete removal of the excipient from the formulation.

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EXHIBIT E

Journal Article

Functionality of Cross-Linked Polyvinylpyrrolidone as a Spheronization Aid: A Promising Alternative t Microcrystalline Cellulose

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Purpose This work seeks to explore and demonstrate the functionality of cross-linked polyvinylpyrrolidone (crospovidone) as a spheronization aid and a promising alternative to microcrystalline cellulose (MCC).

Methods Pellets were prepared with various grades of crospovidone using both small- and large-scale extrusion–spheronization. A Box-Behnken experimental design was employed to elucidate the effects of operating variables on the quality of the pellets. Size and shape analyses of these pellets were conducted and compared to those prepared using MCC.

Results Crospovidone was believed to behave like a liquid repository in its interaction with water during extrusion–spheronization, although its binding ability was weaker than that of MCC. Spherical pellets of narrow size distribution could be made from the finer crospovidone grades with different lactose grades. However, crospovidone-based formulations required higher water levels than weight-equivalent MCC-based formulations. Crospovidone pellets were of equivalent quality to those prepared with MCC, especially in the shape, size, and yield.

Conclusions Crospovidone can be successfully employed as a spheronization aid to produce good pellets without the need of a binder, unlike most of the previously proposed materials. This study exemplified the enormous potential of crospovidone to serve as a competent alternative to MCC in the production of pellets by extrusion–spheronization.

Key Words cross-linked polyvinylpyrrolidone - extrusion–spheronization - microcrystalline cellulose - pellets - spheronization aid

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EXHIBIT 25

Manual of PATENT EXAMINING PROCEDURE

Original Eighth Edition, August 2001
Latest Revision August 2006

U.S. DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

After the examiner reviews the IDS for compliance with 37 CFR 1.97 and 1.98, the examiner should: (See MPEP § 609.05).

(A) Consider the information properly submitted in an IDS in the same manner that the examiner considers other documents in Office search files while conducting a search of the prior art in a proper field of search.

(1) For e-IDS, use the e-IDS icon on examiner's workstation to consider cited U.S. patents and U.S. patent application publications. See MPEP § 609.07 for more information on e-IDS.

(2) Initial the blank column next to the citation to indicate that the information has been considered by the examiner.

(B) Draw a line through the citation to show that it has not been considered if the citation fails to comply with all the requirements of 37 CFR 1.97 and 37 CFR 1.98. - The examiner should inform applicant the reasons why a citation was not considered.

(C) Write "not considered" on an information disclosure statement if none of the information listed complies with the requirements of 37 CFR 1.97 and 37 CFR 1.98. - The examiner will inform applicant the reasons why the IDS was not considered by using form paragraphs 6.49 through 6.49.09.

(D) Sign and date the bottom of the IDS listing.

(E) Ensure that a copy of the IDS listing that is signed and dated by the examiner is entered into the file and mailed to applicant.

>For discussion of electronic processing of IDS, see MPEP § 609.08.<

609.02 Information Disclosure Statements in Continued Examinations or Continuing Applications [R-5]

>When filing a continuing application that claims benefit under 35 U.S.C. 120 to a parent application (other than an international application that designated the U.S.), it will not be necessary for the applicant to submit an information disclosure statement in the continuing application that lists the prior art cited by the examiner in the parent application unless the applicant desires the information to be printed on the patent issuing from the continuing application (for continued prosecution applications filed under 37 CFR 1.53(d), see subsection A.1. below). The examiner of the continuing application will consider information which has been considered by the Office in the parent application.

When filing a continuing application that claims benefit under 35 U.S.C. 120 to an international application that designated the U.S. (see MPEP § 1895), it will be necessary for the applicant to submit an information disclosure statement complying with 37 CFR 1.97 and 1.98 in the continuing application listing the documents cited in the international search report and/or the international preliminary examination report of the international application if applicant wishes to ensure that the information be considered by the examiner in the continuing application.<

IDS IN CONTINUED EXAMINATIONS OR CONTINUING APPLICATIONS

A. IDS That Has Been Considered (1) in the Parent Application, or (2) Prior to the Filing of a Request for Continued Examination (RCE)

1. Continued Prosecution Applications (CPAs) Filed Under 37 CFR 1.53(d)

Information which has been considered by the Office in the parent application of a continued prosecution application (CPA) filed under 37 CFR 1.53(d) will be part of the file before the examiner and need not be resubmitted in the continuing application to have the information considered and listed on the patent.

2. Continuation Applications, Divisional Applications, or Continuation-in-Part Applications Filed Under 37 CFR 1.53(b)

The examiner will consider information which has been considered by the Office in a parent application when examining: (A) a continuation application filed under 37 CFR 1.53(b), (B) a divisional application filed under 37 CFR 1.53(b), or (C) a continuation-in-part application filed under 37 CFR 1.53(b). A listing of the information need not be resubmitted in the continuing application unless the applicant desires the information to be printed on the patent.

If resubmitting a listing of the information, applicant should submit a new listing that complies

with the format requirements in 37 CFR 1.98(a)(1). Applicants are strongly discouraged from submitting a list that includes copies of PTO/SB/08 ** or PTO-892 forms from other applications. A completed PTO/SB/08 ** form from another application may already have initials of an examiner and the application number of another application. This information will likely confuse the record. Furthermore, when the spaces provided on the form have initials of an examiner, there are no spaces available next to the documents listed for the examiner of the subsequent application to provide his or her initials, and the previously relevant initials may be erroneously construed as being applied for the current application.

3. Requests for Continued Examination (RCE) Under 37 CFR 1.114

Information which has been considered by the Office in the application before the filing of a RCE will be part of the file before the examiner and need not be resubmitted to have the information considered by the examiner and listed on the patent.

B. IDS That Has Not Been Considered (1) in the Parent Application, or (2) Prior to the Filing of a Request for Continued Examination

1. Continued Prosecution Applications Filed Under 37 CFR 1.53(d)

Information filed in the parent application that complies with the content requirements of 37 CFR 1.98 will be considered by the examiner in the CPA. No specific request from the applicant that the previously submitted information be considered by the examiner is required.

2. Continuation Applications, Divisional Applications, or Continuation-In-Part Applications Filed Under 37 CFR 1.53(b)

For these types of applications, in order to ensure consideration of information previously submitted, but not considered, in a parent application, applicant must resubmit the information in the continuing application in compliance with 37 CFR 1.97 and 37 CFR 1.98. Pursuant to 37 CFR 1.98(d), if the IDS submitted in the parent application complies with 37 CFR 1.98(a) to (c), copies of the patents, publications, pending U.S. applications, or other information submitted in the parent application need not be resubmitted in the continuing application.

When resubmitting a listing of the information, applicant should submit a new listing that complies with the format requirements in 37 CFR 1.98(a)(1). Applicants are strongly discouraged from submitting a list that includes copies of PTO/SB/08 ** or PTO-892 forms from other applications. A PTO/SB/08 ** form from another application may already have the application number of another application. This information will likely confuse the record.

3. Requests for Continued Examination Under 37 CFR 1.114

Information filed in the application in compliance with the content requirements of 37 CFR 1.98 before the filing of a RCE will be considered by the examiner after the filing of the RCE. For example, an applicant filed an IDS in compliance with 37 CFR 1.98 after the mailing of a final Office action, but the IDS did not comply with the requirements of 37 CFR 1.97(d)(1) and (d)(2) and therefore, the IDS was not considered by the examiner. After applicant files a RCE, the examiner will consider the IDS filed prior to the filing of the RCE. For more details on RCE, see MPEP § 706.07(h).

**>

609.03 Information Disclosure Statements in National Stage Applications [R-3]

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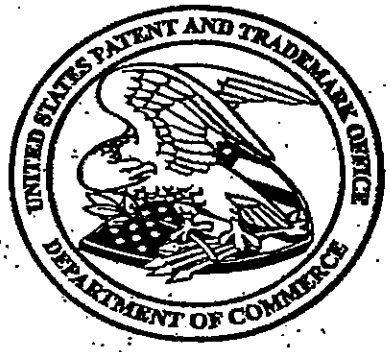
The examiner will consider the documents cited in the international search report in a PCT national stage application when the Form PCT/DO/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage file. In such a case, the examiner should consider the documents from the international search report and indicate by a statement in the first Office action that the information has been considered. There is no requirement that the examiner list the documents on a PTO-892 form.

In a national stage application, the following form paragraphs may be used where appropriate to notify applicant regarding references listed in the search report of the international application:

EXHIBIT 26

Manual of PATENT EXAMINING PROCEDURE

Original Eighth Edition, August 2001
Latest Revision August 2006



U.S. DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

707.01 Primary Examiner Indicates Action for New Assistant [R-2]

After the search has been completed, action is taken in the light of the references found. Where the assistant examiner has been in the Office but a short time, it is the duty of the primary examiner to review the application thoroughly. The usual procedure is for the assistant examiner to explain the invention and discuss the references which he or she regards as most pertinent. The primary examiner may indicate the action to be taken, whether restriction or election of species is to be required, or whether the claims are to be considered on their merits. If action on the merits is to be given, the >primary< examiner may indicate how the references are to be applied in cases where the claim is to be rejected, or authorize allowance if it is not met in the references and no further field of search is known.

707.02 Applications Up for Third Action and 5-Year Applications [R-2]

The supervisory patent examiners should impress their assistants with the fact that the shortest path to the final disposition of an application is by finding the best references on the first search and carefully applying them.

The supervisory patent examiners are expected to personally check on the pendency of every application which is up for the third or subsequent *>Office< action with a view to finally concluding its prosecution.

Any application that has been pending five years should be carefully studied by the supervisory patent examiner and every effort >should be< made to terminate its prosecution. In order to accomplish this result, the application is to be considered "special" by the examiner.

707.05 Citation of References [R-3]

37 CFR 1.104. Nature of examination.

*****

(d) *Citation of references.*

(1) If domestic patents are cited by the examiner, their numbers and dates, and the names of the patentees will be stated. If domestic patent application publications are cited by the examiner, their publication number, publication date, and the names of the applicants will be stated. If foreign published applications or patents are cited, their nationality or country, numbers and dates, and the names of the patentees will be stated, and such other data will be furnished as may be necessary to enable the applicant, or in the case of a reexamination proceeding, the patent owner, to identify the published applications or patents cited. In citing foreign published applications or patents, in case only a part of the document is involved, the particular pages and sheets containing the parts relied upon will be identified. If printed publications are cited, the author (if any), title, date, pages or plates, and place of publication, or place where a copy can be found, will be given.

(2) When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

*****

During the examination of an application or reexamination of a patent, the examiner should cite appropriate prior art which is nearest to the subject matter defined in the claims. When such prior art is cited, its pertinence should be explained.

The examiner must consider all the prior art references (alone and in combination) cited in the application or reexamination, including those cited by the applicant in a properly submitted Information Disclosure Statement. See MPEP § 609.

Form paragraph 7.96 may be used as an introductory sentence.

¶ *7.96 Citation of Relevant Prior Art*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. [1]

Examiner Note:

When such prior art is cited, its relevance should be explained in bracket 1 in accordance with MPEP § 707.05.

Effective June 8, 1995, Public Law 103-465 amended 35 U.S.C. 154 to change the term of a patent to 20 years measured from the filing date of the earliest U.S. application for which benefit under 35 U.S.C. 120, 121 or 365(c) is claimed. The 20-year patent term applies to all utility and plant patents issued on applications filed on or after June 8, 1995. As a result of the 20-year patent term, it is expected, in certain circumstances, that applicants may cancel their claim to priority by amending the specification to delete any references to prior applications. Therefore, examiners should search all applications based on the actual U.S. filing date of the application rather

than on the filing date of any parent U.S. application for which priority is claimed. Examiners should cite of interest all material prior art having an effective filing date after the filing date of the U.S. parent application but before the actual filing date of the application being examined.

Allowed applications should generally contain a citation of pertinent prior art for printing in the patent, even if no claim presented during the prosecution was considered unpatentable over such prior art. Only in those instances where a proper search has not revealed any prior art relevant to the claimed invention is it appropriate to send an application to issue with no art cited. In the case where no prior art is cited, the examiner must write "None" on a form PTO-892 and insert it in the file wrapper. For Image File Wrapper (IFW) processing, see IFW Manual section 3.7. Where references have been cited during the prosecution of parent applications and a continuing application, having no newly cited references, is ready for allowance, the cited references of the parent applications should be listed on a form PTO-892. The form should then be placed in the file of the continuing application. For Image File Wrapper (IFW) processing, see IFW Manual section 3.7. See MPEP § 1302.12. In a continued prosecution application filed under 37 CFR 1.53(d), it is not necessary to prepare a new form PTO-892 since the form from the parent application is in the same file wrapper and will be used by the printer.

In all continuation and continuation-in-part applications, the parent applications should be reviewed for pertinent prior art.

Applicants and/or applicants' *>attorneys< in PCT related national applications may wish to cite the material citations from the PCT International Search Report by an information disclosure statement under 37 CFR 1.97 and 1.98 in order to ensure consideration by the examiner.

In those instances where no information disclosure statement has been filed by the applicant and where documents are cited in the International Search Report but neither a copy of the documents nor an English translation (or English family member) is provided, the examiner may exercise discretion in deciding whether to take necessary steps to obtain the copy and/or translation.

Copies of documents cited will be provided as set forth in MPEP § 707.05(a). That is, copies of documents cited by the examiner will be provided to applicant *except* where the documents:

(A) are cited by applicant in accordance with MPEP § 609, § 707.05(b), and § 708.02;

(B) have been referred to in applicant's disclosure statement;

(C) are cited and have been provided in a parent application;

(D) are cited by a third party in a submission under 37 CFR 1.99 (MPEP § 1134.01); or

(E) are U.S. Patents or U.S. application publications **.

See MPEP § 707.05(e) regarding data used in citing references.

707.05(a) Copies of Cited References [R-3]

Copies of cited >foreign patent documents and nonpatent literature< references (except as noted below) are automatically furnished without charge to applicant together with the Office action in which they are cited. Copies of the cited references are also placed in the application file for use by the examiner during the prosecution.>Copies of U.S. patents and U.S. patent application publications are not provided in paper to applicants and are not placed in the application file.<

Copies of references cited by applicant in accordance with MPEP § 609, § 707.05(b) and § 708.02 are *not* furnished to applicant with the Office action. Additionally, copies of references cited in continuation applications if they had been previously cited in the parent application are not furnished. The examiner should check the left hand column of form PTO-892 if a copy of the reference is not to be furnished to the applicant.

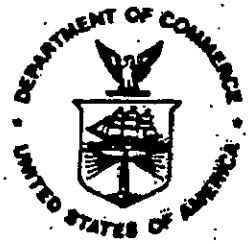
Copies of foreign patent documents and nonpatent literature (NPL) which are cited by the examiner at the time of allowance will be furnished to applicant with the Office action, and copies of the same will also be retained in the file. For Image File Wrapper (IFW) processing, see IFW Manual section 3.7. This will apply to all allowance actions, including first action allowances and *Ex Parte Quayle* actions.

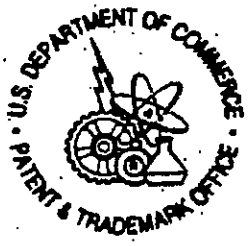
In the rare instance where no art is cited in a continuing application, all the references cited during the prosecution of the parent application will be listed at allowance for printing in the patent.

EXHIBIT 27

Manual of PATENT EXAMINING PROCEDURE

Original Seventh Edition, July 1998





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Telephone: 703–308–9660

Additions to the text of the Manual are indicated by arrows (> <) inserted in the text. Deletions are indicated by a single asterisk (*) where a single word was deleted and by two asterisks (**) where more than one word was deleted. The use of three or five asterisks in the body of the laws and rules indicates a portion of the law or rule which was not reproduced.

First Edition, November 1949
Second Edition, November 1953
Third Edition, November 1961
Fourth Edition, June 1979
Fifth Edition, August 1983
Sixth Edition, January 1995
Seventh Edition, July 1998

Examiner Note:

This form paragraph must be used whenever an application filed on or after September 23, 1996 contains a computer program listing consisting of a paper printout appendix of more than ten pages.

Copies of publicly available computer program listings are available from the Patent and Trademark Office on paper and on microfiche at the cost set forth in 37 CFR 1.19(a).

OTHER INFORMATION

The micrographic standards are set forth in 36 CFR Part 1230.

A microfiche filed with a patent application will be referred to as a "Microfiche Appendix," and will be identified as such on the front page of the patent but will not be part of the printed patent. "Microfiche Appendix" denotes the total microfiche, whether only one or two or more. One microfiche is equivalent to a maximum of either 63 (9x7) or 98 (14x7) frames (pages), or less.

The face of the file wrapper will bear a label to denote that a Microfiche Appendix is included in the application. A statement must be included in the specification to the effect that a microfiche appendix is included in the application. The specification entry must appear at the beginning of the specification immediately following any cross–reference to related applications. 37 CFR 1.77 (a)(6). The patent front page and the *Official Gazette* entry will both contain information as to the number of microfiche and frames of computer program listings appearing in the microfiche appendix.

When an application containing microfiche is received in the Office of Initial Patent Examination (OIPE), a special envelope will be affixed to the right side of the file wrapper underneath all papers, and the microfiche inserted therein. The application file will then proceed on its normal course. A label which sticks up above the file wrapper will be placed at the center section of the face of the wrapper by OIPE. When the application file reaches the Micrographics Division, the Microfiche Appendix label will be placed on the face of the file wrapper. When the Publishing Division of the Office of Patent Publication receives the application file, the person placing the patent number on the face of the file, upon seeing the Microfiche Appendix label, will give the file to the Supervisor who will call Micrographics Division and give the application number and patent number, and request copies of the microfiche. Micrographics Division personnel will then put the patent number on the microfiche(s), making certain each microfiche is the most recent, and numbering each correctly, e.g., 1 of 1, 1 of 2, etc. Upon completion, two copies will be produced and provided to Publishing Division — one for the grant head and one for the file wrapper.

At the time of assembly, the Microfiche Appendix will be placed inside the grant head behind the patent grant for eyeletting, ribboning, and mailing to the patentee/attorney. During the signing of the grant heads by the Attesting Officer, the patent will be checked to assure proper assembly prior to mailing.

609 Information Disclosure Statement

37 CFR 1.97. Filing of information disclosure statement.

(a) In order for an applicant for a patent or for a reissue of a patent to have an information disclosure statement in compliance with § 1.98 considered by the Office during the pendency of the application, it must satisfy paragraph (b), (c), or (d) of this section.

(b) An information disclosure statement shall be considered by the Office if filed by the applicant:

(1) Within three months of the filing date of a national application;

(2) Within three months of the date of entry of the national stage as set forth in § 1.491 in an international application; or

(3) Before the mailing date of a first Office action on the merits,

whichever event occurs last.

(c) An information disclosure statement shall be considered by the Office if filed by the applicant after the period specified in paragraph (b) of this section, provided that the information disclosure statement is filed before the mailing date of either a final action under § 1.113, or a notice of allowance under § 1.311, whichever occurs first, and is accompanied by either:

(1) A statement as specified in paragraph (e) of this section; or

(2) The fee set forth in § 1.17(p).

(d) An information disclosure statement shall be considered by the Office if filed by the applicant after the period specified in paragraph (c) of this section, provided that the information disclosure statement is filed on or before payment of the issue fee and is accompanied by:

(1) A statement as specified in paragraph (e) of this section;

(2) A petition requesting consideration of the information disclosure statement; and

(3) The petition fee set forth in § 1.17(i).

(e) A statement under this section must state either:

(1) That each item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

(2) That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the statement after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

(f) No extensions of time for filing an information disclosure statement are permitted under § 1.136. If a bona fide attempt is made to

comply with §1.98, but part of the required content is inadvertently omitted, additional time may be given to enable full compliance.

(g) An information disclosure statement filed in accordance with this section shall not be construed as a representation that a search has been made.

(h) The filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in § 1.56(b).

(i) Information disclosure statements, filed before the grant of a patent, which do not comply with this section and § 1.98 will be placed in the file, but will not be considered by the Office.

37 CFR 1.98. Content of information disclosure statement.

(a) Any information disclosure statement filed under § 1.97 shall include:

(1) A list of all patents, publications or other information submitted for consideration by the Office;

(2) A legible copy of:

(i) Each U.S. and foreign patent;

(ii) Each publication or that portion which caused it to be listed; and

(iii) All other information or that portion which caused it to be listed, except that no copy of a U.S. patent application need be included; and

(3) A concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language. The concise explanation may be either separate from the specification or incorporated therein.

(b) Each U.S. patent listed in an information disclosure statement shall be identified by patentee, patent number and issue date. Each foreign patent or published foreign patent application shall be identified by the country or patent office which issued the patent or published the application, an appropriate document number, and the publication date indicated on the patent or published application. Each publication shall be identified by author (if any), title, relevant pages of the publication, date and place of publication.

(c) When the disclosures of two or more patents or publications listed in an information disclosure statement are substantively cumulative, a copy of one of the patents or publications may be submitted without copies of the other patents or publications provided that a statement is made that these other patents or publications are cumulative. If a written English-language translation of a non-English language document, or portion thereof, is within the possession, custody or control of, or is readily available to any individual designated in § 1.56(c), a copy of the translation shall accompany the statement.

(d) A copy of any patent, publication or other information listed in an information disclosure statement is not required to be provided if it was previously cited by or submitted to the Office in a prior application, provided that the prior application is properly identified in the statement and relied upon for an earlier filing date under 35 U.S.C. 120.

MINIMUM REQUIREMENTS FOR AN INFORMATION DISCLOSURE STATEMENT

Information Disclosure Statements are not permitted in provisional applications filed under 35 U.S.C. 111(b). Since no substantive examination is given in provisional applications, a disclosure of information is unnecessary. Any such statement filed in a provisional application will be returned or destroyed at the option of the Office. In applications filed under 35 U.S.C. 111(a), applicants and other individuals substantively involved with the preparation and/or prosecution of the application have a duty to submit to the Office information which is material to patentability as defined in 37 CFR 1.56. These individuals also may want the Office to consider information for a variety of other reasons; e.g., without first determining whether the information meets any particular standard of materiality, or because another patent office considered the information to be relevant in a counterpart or related patent application filed in another country, or to make sure that the examiner has an opportunity to consider the same information that was considered by the individuals that were substantively involved with the preparation or prosecution of a patent application.

An information disclosure statement filed in accordance with the provisions of 37 CFR 1.97 and 37 CFR 1.98 provides the procedure available to an applicant to submit information to the Office so that the information will be considered by the examiner assigned to the application. The requirements for the content of a statement have been simplified in the rules which became effective on March 16, 1992, to encourage individuals associated in a substantive way with the filing and prosecution of a patent application to submit information to the Office so the examiner can determine its relevance to the claimed invention. The procedures for submitting an information disclosure statement under the rules are designed to encourage individuals to submit information to the Office promptly.

In order to have information considered by the Office during the pendency of a patent application, an information disclosure statement in compliance with 37 CFR 1.98 as to content must be filed in accordance with the procedural requirements of 37 CFR 1.97. The requirements as to content are discussed in A below. The requirements based on the time of filing the statement are discussed in B below. Examiner handling of information disclosure statements is discussed in C below.

The Office has set forth the minimum requirements for information to be considered in 37 CFR 1.97 and 37 CFR 1.98. Once the minimum requirements are met, the examiner has an obligation to consider the information. These rules provide certainty for the public by de-

fining the requirements for submitting information to the Office so that the Office will consider information before a patent is granted. Information submitted to the Office that does not comply with the requirements of 37 CFR 1.97 and 37 CFR 1.98 will not be considered by the Office but will be placed in the application file.

The filing of an information disclosure statement shall not be construed as a representation that a search has been made. 37 CFR 1.97(g). There is no requirement that an applicant for a patent make a patentability search. Further, the filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in 37 CFR 1.56(b). 37 CFR 1.97(h). See MPEP § 2129 regarding admissions by applicant.

Multiple information disclosure statements may be filed in a single application, and they will be considered, provided each is in compliance with the appropriate requirements. Use of form PTO–1449, "Information Disclosure Citation," or PTO/SB/08A and 08B, "Information Disclosure Statement," is encouraged as a means to provide the required list of information. See C(2) below.

Information which has been considered by the Office in the parent application of a continued prosecution application (CPA) filed under 37 CFR 1.53(d) or a file wrapper continuing application (FWC) filed prior to December 1, 1997 under former 37 CFR 1.62 will be part of the file before the examiner and need not be resubmitted in the continuing application to have the information considered and listed on the patent. Likewise, the examiner will consider information which has been considered by the Office in a parent application when examining (A) a continuation application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, (B) a divisional application filed under 37 CFR 1.53(b) or filed under former 37 CFR 1.60, or (C) a continuation–in–part application (see MPEP § 201.06(b)) filed under 37 CFR 1.53(b), and a list of the information need not be submitted in the continuation, divisional, or continuation–in–part application unless applicant desires the information to be printed on the patent.

The examiner will consider the documents cited in the international search report in a PCT national stage application when the Form PCT/DO/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage file. In such a case, the examiner should consider the documents from the international search report and indicate by a statement in the first Office action that the information has been considered. There is no requirement that the examiner list the documents on a PTO–892 form.

In a national stage application, the following form paragraphs may be used where appropriate to notify applicant regarding references listed in the search report of the international application:

¶ *6.53 References Considered in 37 U.S.C. 371 Application Based Upon Search Report – Prior to Allowance*

The references cited in the Search Report [1] have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO–1449 form, must be filed within the set period for reply to this Office action.

Examiner Note:

1. This form paragraph may be used for PCT National Stage applications submitted under 35 USC 371 where the examiner has obtained copies of the cited references. For applications filed from US, JPO or EPO search authorities, the copies of the references should be supplied by those offices under the trilateral agreement. However, if receipt of such copies is not indicated on the PCT/DO/EO/903 form in the file, burden is on the applicant to supply copies for consideration. See MPEP § 1893.03(g).
2. Instead of using this form paragraph, the examiner may list the references on a PTO–892, thereby notifying the applicant that the references have been considered and will be printed on any patent resulting from this application.
3. This form paragraph should only be used prior to allowance when a statutory period for reply is being set in the Office action.
4. If the application is being allowed, form paragraph 6.54 should be used with the Notice of Allowance instead of this form paragraph.

¶ *6.54 References Considered in 37 U.S.C. 371 Application Based Upon Search Report – Ready for Allowance*

The references cited in the Search Report [1] have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO–1449 form, must be filed within ONE MONTH of the mailing date of this communication. NO EXTENSION OF TIME WILL BE GRANTED UNDER EITHER 37 CFR 1.136(a) OR (b) to comply with this requirement.

Examiner Note:

1. See the Examiner Note for form paragraph 6.53.

¶ *6.55 References Not Considered in 37 U.S.C. 371 Application Based Upon Search Report*

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of each U.S. and foreign patent, each publication or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609 A(1) states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the

707.01 Primary Examiner Indicates Action for New Assistant

After the search has been completed, action is taken in the light of the references found. Where the assistant examiner has been in the Office but a short time, it is the duty of the primary examiner to go into the case thoroughly. The usual procedure is for the assistant examiner to explain the invention and discuss the references which he or she regards as most pertinent. The primary examiner may indicate the action to be taken, whether restriction or election of species is to be required, or whether the claims are to be considered on their merits. If action on the merits is to be given, the examiner may indicate how the references are to be applied in cases where the claim is to be rejected, or authorize allowance if it is not met in the references and no further field of search is known.

707.02(a) Applications Up for Third Action and 5–Year Applications

The supervisory patent examiners should impress their assistants with the fact that the shortest path to the final disposition of an application is by finding the best references on the first search and carefully applying them.

The supervisory patent examiners are expected to personally check on the pendency of every application which is up for the third or subsequent official action with a view to finally concluding its prosecution.

Any application that has been pending five years should be carefully studied by the supervisory patent examiner and every effort made to terminate its prosecution. In order to accomplish this result, the application is to be considered "special" by the examiner.

707.05 Citation of References

37 CFR 1.104. Nature of examination.

*****

(d) *Citation of references.*

(1) If domestic patents are cited by the examiner, their numbers and dates, and the names of the patentees must be stated. If foreign published applications or patents are cited, their nationality or country, numbers and dates, and the names of the patentees must be stated, and such other data must be furnished as may be necessary to enable the applicant, or in the case of a reexamination proceeding, the patent owner, to identify the published applications or patents cited. In citing foreign published applications or patents, in case only a part of the document is involved, the particular pages and sheets containing the parts relied upon must be identified. If printed publications are cited, the author (if any), title, date, pages or plates, and place of publication, or place where a copy can be found, shall be given.

(2) When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

During the examination of an application or reexamination of a patent, the examiner should cite appropriate prior art which is nearest to the subject matter defined in the claims. When such prior art is cited, its pertinence should be explained.

The examiner must fully consider all the prior art references (alone and in combination) cited in the application or reexamination, including those cited by the applicant in a properly submitted Information Disclosure Statement.

Form Paragraph 7.96 may be used as an introductory sentence.

¶ *7.96 Citation of Relevant Prior Art*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. [1]

Examiner Note:

When such prior art is cited, its relevance should be explained in bracket 1 in accordance with MPEP § 707.05.

Effective June 8, 1995, Public Law 103–465 amended 35 U.S.C. 154 to change the term of a patent to 20 years measured from the filing date of the earliest U.S. application for which benefit under 35 U.S.C. 120, 121 or 365(c) is claimed. The 20–year patent term applies to all utility and plant patents issued on applications filed on or after June 8, 1995. As a result of the 20–year patent term, it is expected, in certain circumstances, that applicants may cancel their claim to priority by amending the specification to delete any references to prior applications. Therefore, examiners should search all applications based on the actual U.S. filing date of the application rather than on the filing date of any parent U.S. application for which priority is claimed. Examiners should cite of interest all material prior art having an effective filing date after the filing date of the U.S. parent application but before the actual filing date of the application being examined.

Allowed applications should generally contain a citation of pertinent prior art for printing in the patent, even if no claim presented during the prosecution was considered unpatentable over such prior art. Only in those

instances where a proper search has not revealed any prior art relevant to the claimed invention is it appropriate to send a case to issue with no art cited. In the case where no prior art is cited, the examiner must write "None" on a form PTO–892 and insert it in the file wrapper. Where references have been cited during the prosecution of parent applications and a continuing application, having no newly cited references, is ready for allowance, the cited references of the parent applications should be listed on a form PTO–892. The form should then be placed in the file of the continuing application. See MPEP § 1302.12. In a continued prosecution application filed under 37 CFR 1.53(d) or a file wrapper continuing application filed under former 37 CFR 1.62, it is not necessary to prepare a new form PTO–892 since the form from the parent application is in the same file wrapper and will be used by the printer.

In all continuation and continuation–in–part applications, the parent applications should be reviewed for pertinent prior art.

Applicants and/or applicants' attorney in PCT related national applications may wish to cite the material citations from the PCT International Search Report by an information disclosure statement under 37 CFR 1.97 and 1.98 in order to ensure consideration by the examiner.

In those instances where no information disclosure statement has been filed by the applicant and where documents are cited in the International Search Report but neither a copy of the documents nor an English translation (or English family member) is provided, the examiner may exercise discretion in deciding whether to take necessary steps to obtain the copy and/or translation.

Copies of documents cited will be provided as set forth in MPEP § 707.05(a). That is, copies of documents cited by the examiner will be provided to applicant *except* where the documents:

(A) are cited by applicant in accordance with MPEP § 609, § 707.05(b), and § 708.02;

(B) have been referred to in applicant's disclosure statement;

(C) are cited and have been provided in a parent application; or

(D) are U. S. Patents which are cited at allowance (MPEP § 1302.04).

707.05(a) Copies of Cited References

Copies of cited references (except as noted below) are automatically furnished without charge to applicant together with the Office action in which they are cited. Copies of the cited references are also placed in the application file for use by the examiner during the prosecution.

Copies of references cited by applicant in accordance with MPEP § 609, § 707.05(b) and § 708.02 are *not* furnished to applicant with the Office action. Additionally, copies of references cited in continuation applications if they had been previously cited in the parent application are not furnished. The examiner should check the left hand column of form PTO–892 if a copy of the reference is not to be furnished to the applicant.

Copies of foreign patent documents and nonpatent literature (NPL) which are cited by the examiner at the time of allowance will be furnished to applicant with the Office action, and copies of the same will also be retained in the file. This will apply to all allowance actions, including first action allowances and *Ex Parte Quayle* actions.

In the rare instance where no art is cited in a continuation application, all the references cited during the prosecution of the parent application will be listed at allowance for printing in the patent.

To assist in providing copies of references, the examiner should:

(A) Write the citation of the references on form PTO–892, "Notice of References Cited";

(B) Place the form PTO–892 in the front of the file wrapper;

(C) Include in the application file wrapper all of the references cited by the examiner which are to be furnished to the applicant and which have been obtained from the classified search file;

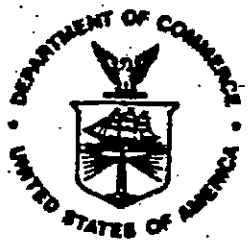
(D) Make two copies of each reference which is to be supplied and which has been located in a place other than the classified search file (e.g., textbooks, bound magazines, personal search material, etc.). Using red ink identify one copy as "File Copy" and the other copy as "Applicant's Copy". Both copies should be placed in the application file wrapper;

(E) Turn the application in to the Technical Support Staff for counting. Any application which is handed in without all of the required references will be

EXHIBIT 28

Manual of PATENT EXAMINING PROCEDURE

Original Sixth Edition, January 1995
Latest Revision July 1996



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First Edition, November 1949
Second Edition, November 1953
Third Edition, November 1961
Fourth Edition, June 1979
Fifth Edition, August 1983
Sixth Edition, January 1995
Revision 1, September 1995
Revision 2, July 1996

The cost of printing long computer programs in patent documents is also very expensive to the Patent and Trademark Office.

In the past, all disclosures forming part of a patent application were presented on paper with the exception of microorganisms. Under 37 CFR 1.96, several different methods for submitting computer program listings, including the use of microfiche, are set forth.

Relatively short computer program listings (10 pages or less) must be submitted on paper and will be printed as part of the patent. If the computer program listing is 11 or more pages in length, it may be submitted on either paper or microfiche, although microfiche is preferred.

Copies of publicly available computer program listings are available from the Patent and Trademark Office on paper and on microfiche at the cost set forth in 37 CFR 1.19(a)(5) and (6).

OTHER INFORMATION

The micrographic standards referred to in 37 CFR 1.96(b)(2) may be obtained from either the National Micrographic Association, 8719 Colesville Road, Silver Spring, Maryland, 20910 or the American National Standards Institute, 1430 Broadway, New York, New York 10018.

The effect of 37 CFR 1.96 is that if a computer program listing (printout) is 11 or more pages long, the applicant may submit such listing in the form of microfiche. Relatively short computer program listings (10 pages or fewer) must be submitted on paper and will be printed as part of the patent, as in the past. When the computer program listing is 11 or more pages in length, it may be submitted on either paper or microfiche, although microfiche is preferred. A microfiche filed with a patent application will be referred to as a "Microfiche Appendix," and will be identified as such on the front page of the patent but will not be part of the printed patent. "Microfiche Appendix," denotes the total microfiche, whether only one or two or more. One microfiche is equivalent to a maximum of either 63 (9x7) or 98 (14x7) frames (pages), or less.

The face of the file jacket will bear a label to denote that a Microfiche Appendix is included in the application. A statement must be included in the specification to the effect that a microfiche appendix is included in the application. The specification entry must appear at the beginning of the specification immediately following any cross-reference to related applications, 37 CFR 1.77(c)(2). The patent front page and the *Official Gazette* entry will both contain information as to the number of microfiche and frames of computer program listings appearing in the microfiche appendix.

When an application containing microfiche is received in the Correspondence and Mail Division, a special pocket will be affixed to the center section of the inside of the file wrapper underneath all papers, and the microfiche inserted therein. The application file will then proceed on its normal course, and when it reaches the Application Branch, a label which sticks up above the file wrapper will be placed at the center section of the face of the wrapper. When the application file reaches the Micrographics Division, the Microfiche Appendix label will be placed on the face of the file wrapper. When the Allowed Files and Assembly Branch of the Office of Publications receives the application file, the person placing the patent number on the face of the file, upon seeing the Microfiche Appendix label, will give the file to the Supervisor who will call Micrographics Division and give the serial number and patent number, and request copies of the microfiche. Micrographics Division personnel will then put the patent number on the microfiche(s), making certain each microfiche is the most recent, and numbering each correctly; e.g., 1 of 1, 1 of 2, etc. Upon completion, two copies will be produced and provided to Allowed and Assembly Branch Files — one for the grant head and one for the file wrapper.

At the time of assembly, the Microfiche Appendix will be placed inside the grant head behind the patent grant for eyeletting, ribboning, and mailing to the patentee/attorney. During the signing of the grant heads by the Attesting Officer, the patent will be checked to assure proper assembly prior to mailing.

609 Information Disclosure Statement [R-2]

37 CFR 1.97. Filing of information disclosure statement.

(a) In order to have information considered by the Office during the pendency of a patent application, an information disclosure statement in compliance with § 1.98 should be filed in accordance with this section.

(b) An information disclosure statement shall be considered by the Office if filed:

(1) Within three months of the filing date of a national application;

(2) Within three months of the date of entry of the national stage as set forth in § 1.491 in an international application; or

(3) Before the mailing date of a first Office action on the merits, whichever event occurs last.

(c) An information disclosure statement shall be considered by the Office if filed after the period specified in paragraph (b) of this section, but before the mailing date of either:

(1) A final action under § 1.113 or

(2) A notice of allowance under §1.311,

whichever occurs first, provided the statement is accompanied by either a certification as specified in paragraph (e) of this section or the fee set forth in § 1.17(p).

(d) An information disclosure statement shall be considered by the Office if filed after the mailing date of either:

(1) A final action under § 1.113 or

(2) A notice of allowance under § 1.311,

whichever occurs first, but before payment of the issue fee, provided the statement is accompanied by:

(i) A certification as specified in paragraph (e) of this section,

(ii) A petition requesting consideration of the information disclosure statement, and

(iii) The petition fee set forth in § 1.17(i)(1).

(e) A certification under this section must state either:

(1) That each item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the statement, or

(2) That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application or, to the knowledge of the person signing the certification after making reasonable inquiry, was known to any individual designated in § 1.56(c) more than three months prior to the filing of the statement.

(f) No extensions of time for filing an information disclosure statement are permitted under § 1.136. If a bona fide attempt is made to comply with §1.98, but part of the required content is inadvertently omitted, additional time may be given to enable full compliance.

(g) An information disclosure statement filed in accordance with this section shall not be construed as a representation that a search has been made.

(h) The filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in § 1.56(b).

(i) Information disclosure statements, filed before the grant of a patent, which do not comply with this section and § 1.98 will be placed in the file, but will not be considered by the Office.

37 CFR 1.98. Content of information disclosure statement.

(a) Any information disclosure statement filed under § 1.97 shall include:

(1) A list of all patents, publications or other information submitted for consideration by the Office;

(2) A legible copy of :

(i) Each U.S. and foreign patent;

(ii) Each publication or that portion which caused it to be listed; and

(iii) All other information or that portion which caused it to be listed, except that no copy of a U.S. patent application need be included; and

(3) A concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language. The concise explanation may be either separate from the specification or incorporated therein.

(b) Each U.S. patent listed in an information disclosure statement shall be identified by patentee, patent number and issue date. Each foreign patent or published foreign patent application shall be identified by the country or patent office which issued the patent or published the application, an appropriate document number, and the publication date indicated on the patent or published application. Each publication shall be identified by author (if any), title, relevant pages of the publication, date and place of publication.

(c) When the disclosures of two or more patents or publications listed in an information disclosure statement are substantively cumulative, a copy of one of the patents or publications may be submitted without copies of the other patents or publications provided that a statement is made that these other patents or publications are cumulative. If a written English—language translation of a non—English language document, or portion thereof, is within the possession, custody or control of, or is readily available to any individual designated in § 1.56(c), a copy of the translation shall accompany the statement.

(d) A copy of any patent, publication or other information listed in an information disclosure statement is not required to be provided if it was previously cited by or submitted to the Office in a prior application, provided that the prior application is properly identified in the statement and relied upon for an earlier filing date under 35 U.S.C. 120.

Information Disclosure Statements are not permitted in provisional applications filed under 35 U.S.C. 111(b). Since no substantive examination is given in provisional applications, a disclosure of information is unnecessary. Any such statement filed in a provisional application will be returned or destroyed at the option of the Office. In applications filed under 35 U.S.C. 111(a), applicants and other individuals substantively involved with the preparation and/or prosecution of the application have a duty to submit to the Office information which is material to patentability as defined in 37 CFR 1.56. These individuals also may want the Office to consider information for a variety of other reasons; e.g., without first determining whether the information meets any particular standard of materiality, or because another patent office considered the information to be relevant in a counterpart or related patent application filed in another country, or to make sure that the examiner has an opportunity to consider the same information that was considered by the individuals that were substantively involved with the preparation or prosecution of a patent application.

An information disclosure statement filed in accordance with the provisions of 37 CFR 1.97 and 1.98 provides the procedure available to an applicant to submit information to the Office so that the information will be considered by the examiner assigned to the application.

The requirements for the content of a statement have been simplified in the new rules which became effective on March 16, 1992, to encourage individuals associated in a substantive way with the filing and prosecution of a patent application to submit information to the Office so the examiner can determine its relevance to the claimed invention. The procedures for submitting an information disclosure statement under the new rules are designed to encourage individuals to submit information to the Office promptly.

In order to have information considered by the Office during the pendency of a patent application, an information disclosure statement in compliance with 37 CFR 1.98 as to content must be filed in accordance with the procedural requirements of 37 CFR 1.97. The requirements as to content are discussed in A below. The requirements based on the time of filing the statement are discussed in B below. Examiner handling of information disclosure statements is discussed in C below.

The Office has set forth the minimum requirements for information to be considered in 37 CFR 1.97 and 1.98. Once the minimum requirements are met, the examiner has an obligation to consider the information. These rules provide certainty for the public by defining the requirements for submitting information to the Office so that the Office will consider information before a patent is granted. Information submitted to the Office that does not comply with the requirements of 37 CFR 1.97 and 1.98 will not be considered by the Office but will be placed in the application file.

The filing of an information disclosure statement shall not be construed as a representation that a search has been made. 37 CFR 1.97(g). There is no requirement that an applicant for a patent make a patentability search. Further, the filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in 37 CFR 1.56(b). 37 CFR 1.97(h). See MPEP § * >2129< regarding admissions by applicant.

Multiple information disclosure statements may be filed in a single application, and they will be considered, provided each is in compliance with the appropriate requirements. Use of form PTO–1449, "Information Disclosure Citation," is encouraged as a means to provide the required list of information. See C(2) below.

Information which is cited or submitted to the Office in the parent application of a file wrapper continuing application under 37 CFR 1.62 will be part of the file before the examiner and need not be resubmitted in the continuing application to have the information considered and listed on the patent. Likewise, the examiner will consider information cited or submitted to the Office in a pa-rent application when examining a continuation or continuation–in–part application (See MPEP § 2001.06(b)) which is not a file wrapper continuing application, and a list of the information need not be submitted in the continuing application unless applicant desires the information to be printed on the patent.

The examiner will consider the documents cited in the international search report in a PCT national stage application, when the Form PCT/DO/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage file. In such a case, the examiner should consider the documents from the international search report and indicate by a statement in the first Office action that the information has been considered. There is no requirement that the examiner list the documents on a PTO–892 form.

A. CONTENT

An information disclosure statement must comply with the provisions of 37 CFR 1.98 as to content in order to be considered by the Office. Each information disclosure statement must comply with the applicable provisions of A(1), A(2), and A(3) below.

A (1) Each information disclosure statement must include a list of all patents, publications, or other information submitted for consideration by the Office.

37 CFR 1.98(b) requires that each U.S. patent listed in an information disclosure statement be identified by patentee, patent number, and issue date. Each foreign patent or published foreign patent application must be identified by the country or patent office which issued the patent or published the application, an appropriate document number, and the publication date indicated on the patent or published application. Each publication must be identified by author (if any), title, relevant pages of the publication, date and place of publication. The date of publication supplied must include at least the month and year of publication, except that the year of publication (without the month) will be accepted if the

707.01 Primary Examiner Indicates Action for New Assistant [R−1]

>After the search has been completed, action is taken in the light of the references found. Where the assistant examiner has been in the Office but a short time, it is the duty of the primary examiner to go into the case thoroughly. The usual procedure is for the assistant examiner to explain the invention and discuss the references which he or she regards as most pertinent. The primary examiner may indicate the action to be taken, whether restriction or election of species is to be required, or whether the claims are to be considered on their merits. If action on the merits is to be given, the examiner may indicate how the references are to be applied in cases where the claim is to be rejected, or authorize allowance if it is not met in the references and no further field of search is known.<

707.02(a) Cases Up for Third Action and 5−Year Cases [R−1]

>The supervisory primary examiners should impress their assistants with the fact that the shortest path to the final disposition of an application is by finding the best references on the first search and carefully applying them.

The supervisory primary examiners are expected to personally check on the pendency of every application which is up for the third or subsequent official action with a view to finally concluding its prosecution.

Any case that has been pending five years should be carefully studied by the supervisory primary examiner and every effort made to terminate its prosecution. In order to accomplish this result, the case is to be considered "special" by the examiner.<

**

707.05 Citation of References [R−2]

During the examination of an application or reexamination of a patent, the examiner should cite appropriate prior art which is nearest to the subject matter defined in the claims. When such prior art is cited, its pertinence should be explained.

Form Paragraph 7.96 may be used as an introductory sentence.

¶ *7.96 Citation of Pertinent Prior Art*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. [1]

Examiner Note:

When such prior art is cited, its pertinence should be explained in accordance with MPEP § 707.05.

Effective June 8, 1995, Public Law 103−465 amended 35 U.S.C. 154 to change the term of a patent to 20 years measured from the filing date of the earliest U.S. application for which benefit under 35 U.S.C. 120, 121 or 365(c) is claimed. The 20−year patent term applies to all utility and plant patents issued on applications filed on or after June 8, 1995. As a result of the 20−year patent term, it is expected, in certain circumstances, that applicants may cancel their claim to priority by amending the specification to delete any references to prior applications. Therefore, examiners should search all applications based on the actual U.S. filing date of the application rather than on the filing date of any parent U.S. application for which priority is claimed. Examiners should cite of interest all material prior art having an effective filing date after the filing date of the U.S. parent application but before the actual filing date of the application being examined.

Allowed applications should generally contain a citation of pertinent prior art for printing in the patent, even if no claim presented during the prosecution was considered unpatentable over such prior art. Only in those instances where a proper search has not revealed any prior art relevant to the claimed invention is it appropriate to send a case to issue with no art cited. In the case where no prior art is cited, the examiner must write "None" on a form PTO−892 and insert it in the file wrapper. Where references have been cited during the prosecution of parent applications and a continuing application, having no newly cited references, is ready for allowance, the cited references of the parent applications should be listed on a form PTO−892. The form should then be placed in the file of the continuing application. See MPEP § 1302.12. In a file wrapper continuing application under 37 CFR 1.62, it is not necessary to prepare a new form PTO−892 since the form from the parent application is in the same file wrapper and will be used by the printer.

In all continuation and continuation−in−part applications, the parent applications should be reviewed for pertinent prior art.

Applicants and/or *>applicants'< attorney in PCT related national applications may wish to cite the material citations from the PCT International Search Report by an information disclosure statement under 37 CFR 1.97 and 1.98 in order to ensure consideration by the examiner.

In those instances where no information disclosure statement has been filed by the applicant and where documents are cited in the International Search Report but neither a copy of the documents nor an English translation (or English family member) is provided, the examiner may exercise discretion in deciding whether to take necessary steps to obtain the copy and/or translation.

Copies of documents cited will be provided as set forth in MPEP § 707.05(a). That is, copies of documents cited by the examiner will be provided to applicant *except* where the documents

A. are cited by applicant in accordance with MPEP § 609, § 707.05(b), and § 708.02,

B. have been referred to in applicant's disclosure statement,

C. are cited and have been provided in a parent application, and

D. are U. S. Patents which are cited at allowance (MPEP § 1302.04).

37 CFR 1.107. Citation of references.

(a) If domestic patents are cited by the examiner, their numbers and dates, and the names of the patentees, and the classes of inventions must be stated. If foreign published applications or patents are cited, their nationality or country, numbers and dates, and the names of the patentees must be stated, and such other data must be furnished as may be necessary to enable the applicant, or in the case of a reexamination proceeding, the patent owner, to identify the published applications or patents cited. In citing foreign published applications or patents, in case only a part of the document is involved, the particular pages and sheets containing the parts relied upon must be identified. If printed publications are cited, the author (if any), title, date, pages or plates, and place of publication, or place where a copy can be found, shall be given.

(b) When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons.

707.05(a) Copies of Cited References [R–1]

>Copies of cited references (except as noted below) are automatically furnished without charge to applicant together with the Office action in which they are cited. Copies of the cited references are also placed in the application file for use by the examiner during the prosecution.

Copies of references cited by applicant in accordance with MPEP § 609, § 707.05(b) and § 708.02 are *not* furnished to applicant with the Office action. Additionally, copies of references cited in continuation applications if they had been previously cited in the parent application are not furnished. The examiner should check the left hand column of form PTO–892 if a copy of the reference is not to be furnished to the applicant.

Copies of foreign patent documents and nonpatent literature (NPL) which are cited by the examiner at the time of allowance will be furnished to applicant with the Office action, and copies of the same will also be retained in the file. This will apply to all allowance actions, including first action allowances and *Ex Parte Quayle* actions.

In the rare instance where no art is cited in a continuation application, all the references cited during the prosecution of the parent application will be listed at allowance for printing in the patent.

To assist in providing copies of references, the examiner should:

(a) Write the citation of the references on form PTO–892, "Notice of References Cited".

(b) Place the form PTO–892 in the front of the file wrapper.

(c) Include in the application file wrapper all of the references cited by the examiner which are to be furnished to the applicant and which have been obtained from the classified search file.

(d) Make two copies of each reference which is to be supplied and which has been located in a place other than the classified search file (i.e. textbooks, bound magazines, personal search material, etc.). Using red ink identify one copy as the "File Copy" and the other copy as the "Applicant's Copy". Both copies should be placed in the application file wrapper.

(e) Turn the application in to the Docket Clerk for counting. Any application which is handed in without all of the required references will be returned to the examiner. The missing reference(s) should be obtained and the file returned to the Docket Clerk as quickly as possible.

EXHIBIT 29

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	C. A. No. 06-222 (JJF)

ANSWERING DECLARATION OF RONALD J. SAWCHUK, Ph.D.

I, Ronald J. Sawchuk, Ph.D., declare as follows:

I am the same Ronald J. Sawchuk, Ph.D., who submitted the Declaration of Ronald J. Sawchuk, Ph.D. ("First Declaration"), which was filed in support of Wyeth's Opening Markman Brief.

I have reviewed the May 8, 2007 declarations of Arthur H. Kibbe, Ph.D. and Bertram A. Spilker, M.D., Ph.D., F.C.P., F.F.P.M., which I understand were filed in support of Impax's Markman brief.

I. Meaning of "Therapeutic Metabolism of Plural Daily Doses"

As I stated on page 9 of my First Declaration, I have considered the meaning of the phrase "a method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride" in claims 21, 24

and 25 of the '171 patent and claims 2, 5 and 6 of the '958 patent. Consistent with my understanding of the plain meaning of the terms in this phrase and the patent specification, the phrase refers to a method in which the extended release formulation is given to a patient over the course of treatment once daily, which results in a rise in venlafaxine plasma concentration, followed by a generally protracted decrease over the rest of the 24 hour period, which eliminates the multiple peaks and troughs in venlafaxine plasma concentration when the same total daily dose of the immediate release dosage form of venlafaxine hydrochloride is administered to a patient two or three times daily. The phrase also means that the plasma levels experienced by a patient treated with an extended release formulation of venlafaxine hydrochloride during a 24 hour period are therapeutic—that is, sufficient to provide relief from the condition being treated over the course of therapy.

In his declaration, Dr. Spilker focused on the phrase "therapeutic metabolism of plural daily doses" in isolation of the rest of the language of the claim and concluded that this phrase is unclear. [Spilker Declaration at ¶¶ 18, 22]. Dr. Kibbe likewise opined in his declaration that although "therapeutic" and "metabolism" each have meanings, one of skill in the art would not clearly understand the meaning of the words in combination. [Kibbe Declaration at ¶¶ 29, 35]. To the contrary, viewed in the context of the claim language at issue--"eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride"--the term "therapeutic metabolism" is specifically

linked to the clinical use of venlafaxine hydrochloride to treat a patient, and thus refers to the metabolic processing of this drug when therapeutic doses of venlafaxine hydrochloride are administered to a patient.

The specification confirms that "therapeutic metabolism" as used in the claims refers to the metabolic processing of venlafaxine over time when therapeutic doses of venlafaxine hydrochloride are administered to a patient:

> In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug.

[Ex. 1, col. 1, line 66 - col. 2, line 7 (emphasis added)]. The above passage indicates that the pattern of therapeutic metabolism associated with immediate release venlafaxine hydrochloride tablets is characterized by a rapid increase in plasma levels of venlafaxine followed by a decrease in the level of the drug over time such that additional dosing is needed after about twelve hours. In contrast, the specification indicates that the claimed extended release venlafaxine hydrochloride formulations eliminate the rapid increase and decrease (sharp peaks and troughs) in plasma drug levels associated with therapeutic administration of an immediate release formulation two or three times daily:

> In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by

> multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets.

Id. at col. 2, lines 24-28.

Thus, in my opinion, one of skill in the art[1] would not have difficulty in understanding the claim phrase "a method for eliminating the troughs and peaks of drug concentration in a patient[']s blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride."

II. Meaning of "With Diminished Incidence[s] of Nausea and Emesis"

In his declaration, Dr. Spilker sets forth an overly-narrow definition of "incidence" as a "rate" or "number of patients who experience an event." [Spilker Declaration at ¶¶ 13-16, 21]. Although I do not disagree that the term "incidence" encompasses the number of patients in a defined population experiencing an event within a defined period of time, the term more broadly encompasses the concepts of frequency, level, and extent. Consistent with my understanding of the plain meaning of this phrase and with the patent specification, the phrase "with diminished incidence(s) of nausea and emesis" refers to reduced frequency (including percent), extent, level, and/or severity of nausea and vomiting in patients taking the extended release venlafaxine hydrochloride dosage form once a day in comparison to that elicited by the same daily dose of immediate release venlafaxine hydrochloride administered two or three times daily.

[1] For purposes of this Declaration, I agree with the definition of a person of ordinary skill in the art set forth in paragraph 11 of the Spilker Declaration.

For example, the Abstract of the invention states that the extended release dosage form "further provides a lower incidence of nausea and vomiting than the conventional tablets." [Abstract. ll. 1-7]. The BRIEF DESCRIPTION OF THE INVENTION states that "The use of the one-a-day (sic) venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing." [Col. 2:46-49]. The reference to reduction by adaptation indicates a reduction in the frequency and severity of nausea and emesis over time among patients who previously experienced one or both side effects. Moreover, the use of "*level* of nausea and *incidence* of emesis" in the specification and the alternative language "incidence(s) of nausea and emesis" in the abstract and claims indicates to me that the drafters intended the terms "level" and "incidence" to be synonymous.

Consistent with this broad usage and with my general understanding of the term, The American Heritage College Dictionary, 3rd Edition, provides a definition of the word "diminish" as "to make smaller or less or to cause to appear so" and defines "incidence" as "extent or frequency of occurrence." [Exhibit A]. Likewise, The Concise Oxford Dictionary of Current English, 5th Edition provides a definition of the word "incidence" as "range, scope, extent, of influence." [Exhibit B]. In contrast to this common usage, the technical references that Dr. Spilker relies on provide definitions of "incidence" that are less descriptive of a reduced frequency of nausea and emesis, or the concept of "adaptation," described in the specification. Thus, for example, a patient

treated with an extended release formulation of venlafaxine hydrochloride who experiences initial nausea and emesis that resolves by the second day of a clinical study plainly has a reduced incidence of nausea and emesis as compared to a patient treated with conventional, immediate release venlafaxine hydrochloride who experiences nausea and emesis each day during the first two weeks of the trial. Although the patient treated with the extended release formulation experiences less frequent nausea and emesis, and adapts more rapidly to these side effects, Dr. Spilker's definition of the term "incidence", which to him means only "a number or rate of patients" (*see* Spilker Declaration at ¶ 21), would consider this patient as equivalent to a patient treated with the immediate release formulation who experiences more frequent and/or severe nausea. Dr. Spilker's overly restrictive definition of "incidence" is inconsistent with both the patents' specification and the real-life experiences of patients who have benefited from the reduction in frequency and severity of nausea and emesis, thanks to the extended release formulation of venlafaxine hydrochloride.

The term incidence, as I view it, is also consistent with how nausea and vomiting data are collected by clinical study investigators.

REDACTED

REDACTED

In view of the above, the term "incidence(s)" as used in the claims is not limited to the number of patients exhibiting nausea or vomiting at least once during the course of a study. Rather, "diminished incidence(s) of nausea and emesis" encompasses not only a reduction in the frequency of those events, but also reductions in the degree (severity, duration, intensity, etc.) of nausea and emesis.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed this 24th day of May 2007, at Prior Lake, Minnesota.

Ronald J. Sawchuk

Ronald J. Sawchuk, Ph.D.

EXHIBIT A

THE AMERICAN HERITAGE COLLEGE DICTIONARY

THIRD EDITION

HOUGHTON MIFFLIN COMPANY
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1.a. A parking light on a motor vehicle. b. Low beam. 2. *Archaic.* Dusk. [ME < OE.] — dim′ly *adv.* — dim′ness *n.*

dim. *abbr.* 1. Dimension. 2. Diminished. 3. *Mus.* Diminuendo. 4. Diminutive.

Di•Mag•gio (də-mä′zhē-ō, -măj′ē-ō), Joseph Paul. "Joltin' Joe." b. 1914. Amer. baseball player considered the best all-around player ever at center field.


Joe DiMaggio

dime (dīm) *n.* 1. A coin of the United States or Canada worth ten cents. 2. *Slang.* A dime bag. —*idioms.* a dime a dozen. Overabundant; commonplace. on a dime. At a precise point; within a narrowly defined area: *a sports car that stops on a dime.* [ME, tenth part < OFr. *disme* < Lat. *decima (pars),* tenth (part) < *decem,* ten. See dekm*.]

dime bag *n. Slang.* A specified amount of an unlawful drug, packaged and sold for a fixed price, usu. about ten dollars.

di•men•hy•dri•nate (dī′mĕn-hī′drə-nāt′) *n.* An antihistamine, $C_{24}H_{28}ClN_5O_3$, used to treat motion sickness and allergies. [DIMETHYL + (AMIN)E(S) + *hydrinate* (HYDR(O)- + (AM)IN(E) + -ATE²).]

dime novel *n.* A melodramatic novel of romance or adventure, usu. in paperback. [After the *Dime Book Series,* pub. by Erastus Flavel Beadle.] — dime novelist *n.*

di•men•sion (dĭ-mĕn′shən, dī-) *n.* 1. A measure of spatial extent, esp. width, height, or length. 2. Extent or magnitude; scope. Often used in the plural. 3. Aspect; element. 4. *Math.* a. One of the least number of independent coordinates required to specify uniquely a point in space or in space and time. b. The range of such a coordinate. 5. *Phys.* A physical property, such as mass, length, time, or a combination thereof, regarded as a fundamental measure or as one of a set of fundamental measures of a physical quantity. — *v.* -sioned, -sion•ing, -sions. 1. To cut or shape to specified dimensions. 2. To mark with specified dimensions. [ME *dimensioun* < Lat. *dīmēnsiō, dīmēnsiōn-,* extent < *dīmēnsus,* p.part. of *dīmētīrī,* to measure out : *dī-, dis-,* dis- + *mētīrī,* to measure; see mē-²*.] — di•men′sion•al *adj.* — di•men′sion•al′i•ty (-shə-năl′ĭ-tē) *n.* — di•men′sion•al•ly *adv.*

di•mer (dī′mər) *n.* 1. A molecule consisting of two identical simpler molecules. 2. A chemical compound consisting of dimers. [DI-¹ + (POLY)MER.] — di•mer′ic (dī-mĕr′ĭk) *adj.*

di•mer•cap•rol (dī′mər-kăp′rôl, -rōl, -rŏl) *n.* An oily viscous liquid, $C_3H_8OS_2$, used as an antidote for poisoning caused by lewisite, organic arsenic compounds, and heavy metals including gold. [DI-¹ + MERCAP(TAN) + (P)R(OPANE) + -OL(E).]

dim•er•ous (dĭm′ər-əs) *adj.* 1. Consisting of two parts or segments, as the tarsus in certain insects. 2. *Bot.* Having flower parts in sets of two. — dim′er•ism *n.*

dime store *n.* See five-and-ten.

dim•e•ter (dĭm′ĭ-tər) *n.* A line of verse consisting of two metrical feet. [LLat. < Gk. *dimetros,* having two meters : *di-,* two; see DI-¹ + *metron,* meter; see METER¹.]

di•meth•yl (dī-mĕth′əl) *n.* An organic compound, esp. ethane, containing two methyl groups.

di•meth•yl•ni•tros•a•mine (dī-mĕth′əl-nī-trō′sə-mēn′, -nī′trō-săm′ēn) *n.* A carcinogenic nitrosamine, $C_2H_6N_2O$, that occurs in tobacco smoke and certain foods.

di•meth•yl•sulf•ox•ide (dī-mĕth′əl-sŭl-fŏk′sīd′) *n.* DMSO.

dimin. *abbr.* 1. *Mus.* Diminuendo. 2. Diminutive.

di•min•ish (dĭ-mĭn′ĭsh) *v.* -ished, -ish•ing, -ish•es. — *tr.* 1.a. To make smaller or less or to cause to appear so. b. To detract from the authority, reputation, or prestige of. 2. To cause to taper. 3. *Mus.* To reduce (a perfect or minor interval) by a semitone. — *intr.* 1. To become smaller or less. See Syns at decrease. 2. To taper. [ME *diminishen,* blend of *diminuen,* to lessen (< OFr. *diminuer* < Lat. *dīminuere,* var. of *dēminuere* : *dē-, de-* + *minuere,* to lessen) and *minishen,* to reduce (< OFr. *menuisier* < VLat. **minūtiāre* < Lat. *minūtia,* smallness < *minūtus,* small < p.part. of *minuere,* to lessen; see mei-²*).] — di•min′ish•a•ble *adj.* — di•min′ish•ment *n.*

di•min•ished capacity (dĭ-mĭn′ĭsht) *n. Law.* Lack of ability to achieve the state of mind necessary for the commission of a particular crime.

di•min•ish•ing returns (dĭ-mĭn′ĭ-shĭng) *pl.n.* A yield rate that after a certain point fails to increase proportionately to additional outlays of capital or investments of time and labor.

di•min•u•en•do (dĭ-mĭn′yōō-ĕn′dō) *n., adv., & adj. Mus.* Decrescendo. [Ital., pr.part. of *diminuire,* to diminish < Lat. *dīminuere.* See DIMINISH.]


dingo
Canis dingo

dim•i•nu•tion (dĭm′ə-nōō′shən, -nyōō′-) *n.* 1.a. The act or process of diminishing. b. The resulting reduction; decrease. 2. *Mus.* Repetition of a theme in notes one-quarter or one-half the duration of the original. [ME *diminucioun* < OFr. *diminution* < Lat. *dīminūtiō, dīminūtiōn-* < *dīminūtus,* p.part. of *dīminuere.* See DIMINISH.] — dim′i•nu′tion•al *adj.*

di•min•u•tive (dĭ-mĭn′yə-tĭv) *adj.* 1. Extremely small in size; tiny. See Syns at small. 2. *Gram.* Of or being a suffix that indicates smallness, youth, familiarity, affection, or contempt, as *-kin* in *lambkin.* — *n.* 1. *Gram.* A diminutive suffix, word, or name. 2. A very small person or thing. [ME *diminutif* < OFr. < Lat. *dīminūtīvus* < *dīminūtus,* p.part. of *dīminuere.* See DIMINISH.] — di•min′u•tive•ly *adv.* — di•min′u•tive•ness *n.*

dim•i•ty (dĭm′ĭ-tē) *n., pl.* -ties. A sheer crisp cotton fa[bric] with raised woven stripes or checks. [ME *demyt* < Med.[Lat.] *dimitum* < Gk. *dimiton* < neut. of *dimitos,* double-thread[ed] : *di-,* two; see DI-¹ + *mitos,* thread.]

dim•mer (dĭm′ər) *n.* 1. A rheostat or other device used to [vary] the intensity of an electric light. 2.a. A parking light o[n a] motor vehicle. b. Low beam.

di•mor•phic (dī-môr′fĭk) also di•mor•phous (-fəs) *adj.* [Ex]isting or occurring in two distinct forms; exhibiting di[mor]phism.

di•mor•phism (dī-môr′fĭz′əm) *n.* 1. *Biol.* The existence [with]in a species of two distinct forms that differ in one or [more] characteristics, such as shape. 2. *Bot.* The occurrence of [two] distinct forms of the same parts in one plant. 3. *Chem.* [&] *Phys.* Dimorphic crystallization.

dim-out (dĭm′out′) *n.* 1. Restricted use of lights at night [to] make a city less visible from the air in wartime. 2. The darkness resulting from restricted use of lights at night.

dim•ple (dĭm′pəl) *n.* 1. A small natural indentation in the [flesh] on a part of the human body, as in the cheek. 2. A [slight] depression or indentation in a surface. — *v.* -pled, -pling, -ples. — *intr.* To form dimples by smiling. — *tr.* To pro[duce] dimples in. [ME *dympull* < OE **dympel.*] — dim′ply *adj.*

dim sum (dĭm′ sōōm′, shŭm′) *n.* A traditional Chinese me[al in] which small portions of a variety of foods, including d[ump]lings, are served in succession. [Chin. (Cantonese) dim sum < Chin. (Mandarin) *diăn xīn,* light refreshments : *diăn,* [dot,] drop + *xīn,* heart, center.]

dim•wit (dĭm′wĭt′) *n. Slang.* A stupid person. — dim′wit[ted] *adj.* — dim′wit′ted•ly *adv.* — dim′wit′ted•ness *n.*

din (dĭn) *n.* A jumble of loud, usu. discordant sounds. See [Syns] at noise. — *v.* dinned, din•ning, dins. — *tr.* 1. To stun [with] deafening noise. 2. To instill by wearying repetition. — *intr.* To make a loud noise. [ME *dine* < OE *dynn.*]

di•nar (dĭ-när′, dē′när′) *n.* 1. See table at currency. 2. [Any of] several units of gold and silver currency formerly used [in the] Middle East. [Ar. *dīnār* < LGk. *dēnarion* < Lat. *dēnārius.* See DENARIUS.]

Di•nar•ic Alps (dĭ-năr′ĭk). A range of the Balkan Pe[ninsula] extending c. 644 km (400 mi) along the E coast of the [Adri]atic Sea.

dine (dīn) *v.* dined, din•ing, dines. — *intr.* To have [dinner.] — *tr.* To give dinner to; entertain at dinner. [ME *dinen* < OFr.] *diner, disner* < VLat. **disiūnāre* < **disiēiūnāre* : Lat.] *dis-* + Lat. *iēiūnium,* fast.]

din•er (dī′nər) *n.* 1. One that dines. 2. See dining car. [3. A] small, usu. inexpensive restaurant with a long coun[ter and] booths housed in a building resembling a dining car.

Di•ne•sen (dē′nə-sən, dĭn′ĭ-), Isak. Baroness Karen [Blixen.] 1885–1962. Danish writer who is best known for he[r] ... *Out of Africa* (1937).

di•nette (dī-nĕt′) *n.* 1. A nook or alcove located in or [near a] kitchen and used for informal meals. 2. The table and [chairs] used to furnish such an area. [DINE + -ETTE.]

ding¹ (dĭng) *v.* dinged, ding•ing, dings. — *intr.* 1. To [ring;] clang. 2. To speak persistently and repetitiously. — *tr.* [1. To] cause to clang. 2. To instill with constant repetition. [— *n.* A] ringing sound. [Partly imit. and partly alteration of ...]

ding² (dĭng) *n. Informal.* A small dent or nick, as in a ... *ding,* to strike, beat on (< ME *dingen;* akin to ON ... and < DENT.)] — ding *v.*

ding-a-ling (dĭng′ə-lĭng) *n. Slang.* A scatterbrained or ... person.

ding•bat (dĭng′băt′) *n.* 1. *Slang.* A stupid or silly ... 2. An object, such as a brick, used as a missile. 3. ... unspecified gadget or other small article. 4. *Print.* ... graphical ornament or symbol. [?]

ding-dong (dĭng′dông′, -dŏng′) *n.* 1. The peal of ... 2. *Slang.* An empty-headed person; a fool. — *intr.v.* ... -dong•ing, -dongs. To ring; jingle. — *adj.* Characteriz[ed by] hammering exchange, as of blows. [Imit.]

din•ghy (dĭng′ē) *n., pl.* -ghies. *Naut.* 1. A small op[en boat] carried as a tender, lifeboat, or pleasure craft on a la[rger ship.] 2. A small rowboat. 3. An inflatable rubber life raft. [... *dingī,* dim. of *dingā,* boat.]

din•gle (dĭng′gəl) *n.* A small wooded valley; a dell. [... hollow.]

Ding Ling (dĭng′ lĭng′). 1904–86. Chinese writer [whose] works explore the role of women in Communist C[hina.]

din•go (dĭng′gō) *n., pl.* -goes. A wild dog (*Canis d*[*ingo*]) of Australia having a reddish-brown or yellowish-bro[wn coat.] [Dharuk (Aboriginal language of SE Australia) ...]

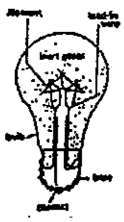
din•gus (dĭng′əs) *n. Slang.* An article whose name is ... or forgotten. [Du., *dinges,* prob. < Ger., genitive ... thing < OHGer.]

din•gy (dĭn′jē) *adj.* -gi•er, -gi•est. 1. Darkened wi[th smoke] and grime; dirty or discolored. 2. Shabby, drab, or ... [Poss. < ME *dinge,* dung, var. of *dung.* See DUNG.] — din′gi•ly *adv.* — din′gi•ness *n.*

din•ing car (dī′nĭng) *n.* A railroad car in which ... served.

dining room *n.* A room in which meals are eaten.

di•min•ish (dĭ-mĭn′ĭsh) *v.* **-ished, -ish•ing, -ish•es.** —*tr.* **1.a.** To make smaller or less or to cause to appear so. **b.** To detract from the authority, reputation, or prestige of. **2.** To cause to taper. **3.** *Mus.* To reduce (a perfect or minor interval) by a semitone. —*intr.* **1.** To become smaller or less. See Syns at **decrease. 2.** To taper. [ME *diminishen*, blend of *diminuen*, to lessen (< OFr. *diminuer* < Lat. *dīminuere*, var. of *dēminuere*: *dē-*, de- + *minuere*, to lessen) and *minishen*, to reduce (< OFr. *minuiser* < VLat. **minūtiāre* < Lat. *minūtia*, smallness < *minūtus*, small < p.part. of *minuere*, to lessen; see mei-[2*]).] —**di•min′ish•a•ble** *adj.* —**di•min′ish•ment** *n.*



incandescent lamp

in•cal•cu•la•ble (in-kăl′kyə-lə-bəl) *adj.* **1.a.** Impossible to calculate: *a mass of incalculable figures.* **b.** Too great to be calculated or reckoned: *incalculable wealth.* **2.** Impossible to foresee; unpredictable. —**in•cal′cu•la•bil′i•ty, in•cal′cu•la•ble•ness** *n.* —**in•cal′cu•la•bly** *adv.*

Syns: incalculable, countless, immeasurable, incomputable, inestimable, infinite, innumerable, measureless. The central meaning shared by these adjectives is "being greater than can be calculated or reckoned": *incalculable riches; countless hours; an immeasurable distance; an incomputable amount; jewels of inestimable value; infinite reasons; innumerable difficulties; measureless power.* Ant: *calculable.*

in•ca•les•cent (in′kə-lĕs′ənt) *adj.* Growing hotter or more ardent. [Lat. *incalēscēns, incalēscent-*, pr.part. of *incalēscere*, to grow warm : *in-*, intensive pref.; see IN-² + *calēscere*, to grow warm, inchoative of *calēre*, to be warm; see **kelə-¹***.] —**in′ca•les′cence** *n.*

in cam•er•a (kăm′ər-ə) *adv.* **1.** In secret; privately. **2.** *Law.* In private with a judge rather than in open court. [NLat. *in camerā* : Lat. *in*, in + Med.Lat. *camerā*, chamber.]

In•can (ing′kən) *adj.* Of or relating to the Inca, their civilization, or their language. —*n.* **1.** An Inca. **2.** Quechua.

in•can•desce (in′kən-dĕs′) *tr. & intr.v.* **-desced, -desc•ing, -desc•es.** To make or become incandescent. [Lat. *incandēscere*, to glow : *in-*, intensive pref.; see IN-² + *candēscere*, to glow, inchoative of *candēre*, to shine; see **kand-***.]

in•can•des•cence (in′kən-dĕs′əns) *n.* **1.** The emission of visible light by a hot object. **2.** The light emitted by such an object. **3.** A high degree of emotion, intensity, or brilliance.

in•can•des•cent (in′kən-dĕs′ənt) *adj.* **1.** Emitting visible light as a result of being heated. **2.** Shining brilliantly; very bright. See Syns at **bright. 3.** Characterized by ardent emotion, intensity, or brilliance. —**in′can•des′cent•ly** *adv.*

incandescent lamp *n.* An electric lamp in which a filament is heated to incandescence by an electric current.

in•can•ta•tion (in′kăn-tā′shən) *n.* **1.** Ritual recitation of charms or spells to produce a magic effect. **2.a.** A formula used in ritual recitation; a charm or spell. **b.** A conventionalized utterance repeated without thought or aptness; a formula. [ME *incantacioun* < OFr. *incantation* < LLat. *incantātiō, incantātiōn-*, spell < Lat. *incantātus*, p.part. of *incantāre*, to enchant. See ENCHANT.] —**in′can•ta′tion•al** *adj.* —**in•can′ta•to′ry** (-tə-tôr′ē, -tōr′ē) *adj.*

in•ca•pa•ble (in-kā′pə-bəl) *adj.* **1.a.** Lacking the necessary ability, capacity, or power: *incapable of love.* **b.** Unable to perform adequately; incompetent. **2.** Not admitting or permitting; not susceptible. **3.** *Law.* Lacking legal qualifications or requirements; ineligible. —**in•ca′pa•bil′i•ty, in•ca′pa•ble•ness** *n.* —**in•ca′pa•bly** *adv.*

in•ca•pac•i•tant (in′kə-păs′ĭ-tənt) *n.* A device or substance, such as tear gas, used to incapacitate individuals temporarily.

in•ca•pac•i•tate (in′kə-păs′ĭ-tāt′) *tr.v.* **-tat•ed, -tat•ing, -tates. 1.** To deprive of strength or ability; disable. **2.** To make legally ineligible; disqualify. —**in′ca•pac′i•ta′tion** *n.*

in•ca•pac•i•ty (in′kə-păs′ĭ-tē) *n., pl.* **-ties. 1.** Inadequate strength or ability; lack of capacity. **2.** A defect or handicap; a disability. **3.** *Law.* Something that renders one incapable.

in•cap•su•late (in-kăp′sə-lāt′) *v.* Var. of **encapsulate.**

in•car•cer•ate (in-kär′sə-rāt′) *tr.v.* **-at•ed, -at•ing, -ates. 1.** To put into jail. **2.** To shut in; confine. [Med.Lat. *incarcerāre, incarcerāt-* : Lat. *in-*, in; see IN-² + Lat. *carcer*, prison.] —**in•car′cer•a′tion** *n.* —**in•car′cer•a′tor** *n.*

in•car•na•dine (in-kär′nə-dīn′, -dēn′, -dĭn) *adj.* **1.** Flesh-colored. **2.** Blood-red. —*tr.v.* **-dined, -din•ing, -dines.** To make incarnadine, esp. to redden. [Fr. *incarnadin* < Ital. *incarnatino*, dim. of *incarnato* : *in*, in (< Lat.; see IN-²) + *carne*, flesh (< Lat. *carō, carn-*; see INCARNATE).]

in•car•nate (in-kär′nĭt) *adj.* **1.a.** Invested with bodily nature and form: *an incarnate spirit.* **b.** Embodied in human form; personified: *a villain who is evil incarnate.* **2.** Incarnadine. —*tr.v.* (-nāt′) **-nat•ed, -nat•ing, -nates. 1.a.** To give bodily, esp. human, form to. **b.** To personify. **2.** To realize in action or fact; actualize. [ME < LLat. *incarnātus*, p.part. of *incarnāre*, to make flesh : Lat. *in-*, causative pref.; see IN-² + Lat. *carō, carn-*, flesh; see **sker-¹***.] —**in•car′na′tor** *n.*

in•car•na•tion (in′kär-nā′shən) *n.* **1.a.** The act of incarnating. **b.** The condition of being incarnated. **2. Incarnation.** *Theol.* The Christian doctrine that the Son of God was conceived in the womb of Mary and that Jesus is true God and true man. **3.** A bodily manifestation of a supernatural being. **4.** One believed to personify a given abstract quality or idea. **5.** A period of time passed in a given bodily form or condition: *hopes for a better life in another incarnation.*

in•case (in-kās′) *v.* Var. of **encase.**

in•cau•tious (in-kô′shəs) *adj.* Not cautious; rash. —**in•cau′tious•ly** *adv.* —**in•cau′tious•ness** *n.*

in•cen•di•ar•y (in-sĕn′dē-ĕr′ē) *adj.* **1.a.** Causing or capable of causing fire. **b.** Of or containing chemicals that produce intensely hot fire when exploded: *an incendiary bomb.* **c.** Of or involving arson. **2.** Tending to inflame; inflammatory. —*n., pl.* **-ies. 1.** An arsonist. **2.** An incendiary device. **3.** One who creates or stirs up factionism or sedition; an agitator. [ME < Lat. *incendiārius* < *incendium*, fire < *incendere*, to set on fire. See INCENSE¹.] —**in•cen′di•a•rism** (-ə-rĭz′əm) *n.*

in•cense¹ (in-sĕns′) *tr.v.* **-censed, -cens•ing, -cens•es.** To cause to be extremely angry; infuriate. [ME *encensen* < OFr. *incenser* < LLat. *incēnsāre*, to sacrifice, burn < Lat. *incēnsus*, p.part. of *incendere*, to set on fire. See **kand-***.]

in•cense² (in′sĕns′) *n.* **1.a.** An aromatic substance, such as wood or a gum, that is burned to produce a pleasant odor. **b.** The smoke or odor produced by the burning of such a substance. **2.** A pleasant smell. **3.** Flattering or fawning attention; homage. —*tr.v.* **-censed, -cens•ing, -cens•es. 1.** To perfume with incense. **2.** To burn incense to, as a ritual offering. [ME *encens* < OFr. < Lat. *incēnsum* < neut. p.part. of *incendere*, to set on fire. See **kand-***.]

incense cedar *n.* Any of several coniferous evergreen trees of the genera *Calocedrus* and *Libocedrus*, having flattened branches with scalelike leaves.

in•cen•tive (in-sĕn′tĭv) *n.* Something, such as a reward or punishment, that induces action or motivates effort. —*adj.* Serving to induce or motivate. [ME < LLat. *incentīvum*, neut. of *incentīvus*, inciting < Lat., setting the tune < *incentus*, p.part. of *incinere*, to sound : *in-*, intensive pref.; see IN-² + *canere*, to sing; see **kan-***.]

in•cept (in-sĕpt′) *tr.v.* **-cept•ed, -cept•ing, -cepts.** To take in; ingest. [Lat. *incipere, incept-*, to begin, take up. See INCEPTION.] —**in•cep′tor** *n.*

in•cep•tion (in-sĕp′shən) *n.* The beginning of something, such as an undertaking; a commencement. See Syns at **origin.** [ME *incepcion* < Lat. *inceptiō, inceptiōn-* < *inceptus*, p.part. of *incipere*, to begin, take up : *in-*, in; see IN-² + *capere*, to take; see **kap-***.]

in•cep•tive (in-sĕp′tĭv) *adj.* **1.** Incipient; beginning. **2.** *Gram.* Inchoative. —*n. Gram.* An inchoative verb.

in•cer•ti•tude (in-sûr′tĭ-to͞od′, -tyo͞od′) *n.* **1.** Uncertainty. **2.** Absence of confidence; doubt. **3.** Insecurity or instability.

in•ces•sant (in-sĕs′ənt) *adj.* Continuing without interruption. See Syns at **continual.** [ME *incessaunte* < LLat. *incessāns, incessant-* : Lat. *in-*, not; see IN-¹ + Lat. *cessāns*, pr.part. of *cessāre*, to stop; see CEASE.] —**in•ces′san•cy** *n.* —**in•ces′sant•ly** *adv.*

in•cest (in′sĕst′) *n.* **1.** Sexual relations between persons so closely related that their marriage is illegal or forbidden by custom. **2.** The statutory crime of sexual relations with such a relative. [ME < Lat. *incestum*, neut. of *incestus*, impure, unchaste : *in-*, not; see IN-¹ + *castus*, pure, chaste; see **kes-***.]

in•ces•tu•ous (in-sĕs′cho͞o-əs) *adj.* **1.** Of, involving, or suggestive of incest. **2.** Having committed incest. **3.** Improperly intimate or interconnected. —**in•ces′tu•ous•ly** *adv.* —**in•ces′tu•ous•ness** *n.*

inch¹ (inch) *n.* **1.** A unit of length in the U.S. Customary and British Imperial systems, equal to 1⁄12 of a foot (2.54 centimeters). See table at **measurement. 2.** A fall, as of rain or snow, sufficient to cover a surface to the depth of one inch. **3.** A unit of atmospheric pressure that is equal to the pressure exerted by a one-inch column of mercury at the earth's surface at a temperature of 0°C. **4.** A very small degree or amount. —*intr. & tr.v.* **inched, inch•ing, inch•es.** To move or cause to move slowly or by small degrees. —*idioms.* **every inch.** In every respect; entirely. **inch by inch.** Very gradually or slowly. **within an inch of.** Almost to the point of. [ME < OE *ynce* < Lat. *uncia*, one twelfth of a unit. See **oi-no-***.]

inch² (inch) *n. Scots.* A small island. [ME < Sc.Gael. *innis* < OIr. *inis.*]

inch•er (in′chər) *n.* Something measuring a specified number of inches. Often used in combination: *an 18-incher.*

inch•meal (inch′mēl′) *adv.* Little by little; gradually. [INCH¹ + (PIECE)MEAL.]

in•cho•ate (in-kō′ĭt) *adj.* **1.** In an initial or early stage; incipient. **2.** Imperfectly formed or developed: *a vague, inchoate idea.* [Lat. *inchoātus*, p.part. of *inchoāre*, to begin, alteration of *incohāre* : *in-*, in; see IN-² + *cohum*, strap from yoke to harness.] —**in•cho′ate•ly** *adv.* —**in•cho′ate•ness** *n.*

in•cho•a•tive (in-kō′ə-tĭv) *adj.* **1.** Beginning; initial. **2.** *Gram.* Of or being a verb or verbal form that designates the beginning of an action, a state, or an event. —**in•cho′a•tive** *n.* —**in•cho′a•tive•ly** *adv.*

In•chon (in′chŏn′). A city of NW South Korea on an inlet of the Yellow Sea SW of Seoul. Pop. 1,387,000.

inch•worm (inch′wûrm′) *n.* See **measuring worm.**

in•ci•dence (in′sĭ-dəns) *n.* **1.** The act or an instance of happening; occurrence. **2.** Extent or frequency of occurrence: *a high incidence of malaria.* **3.** *Phys.* **a.** The arrival of radiation or a projectile at a surface. **b.** Angle of incidence.

in•ci•dent (in′sĭ-dənt) *n.* **1.** A definite and separate occurrence; an event. See Syns at **occurrence. 2.** A usu. minor event or condition subordinate to another. **3.** Something contingent on or related to something else. **4.** An occurrence or event that interrupts normal procedure or precipitates a crisis: *an international incident.* —*adj.* **1.** Tending to arise or occur as a result or an accompaniment. **2.** Related to or dependent on another thing. **3.** *Phys.* Falling upon or striking a surface: *incident radiation.* [ME < OFr., apt to happen, an incident <

Lat. *incidēns, incident-*, pr.part. of *incid*
in; see IN-² + *cadere*, to fall; see **kad-***
in•ci•den•tal (in′sĭ-dĕn′tl) *adj.* **1.** Occur
or as an unpredictable or minor accor
minor, casual, or subordinate nature:
—*n.* A minor accompanying item or exp
in•ci•den•tal•ly (in′sĭ-dĕn′tl-ē) *adv.* **1.** A
dinate matter: *a lawyer and incidentally*
-dĕnt′lē). Apart from the main subject;
incidental music *n. Mus.* Music accomp
dialogue of a drama or filling intervals be
in•cin•er•ate (in-sĭn′ə-rāt′) *v.* **-at•ed, -**
To cause to burn to ashes. —*intr.* To bu
Lat. *incinerāre, incinerāt-* : Lat. *in-*, cau
+ Lat. *cinis, ciner-*, ashes.] —**in•cin′er**
in•cin•er•a•tor (in-sĭn′ə-rā′tər) *n.* One
an apparatus, such as a furnace, for bur
in•cip•i•ent (in-sĭp′ē-ənt) *adj.* Beginning
detecting incipient tumors. [Lat. *incipiēn*
of *incipere*, to begin. See INCEPTION.] —
cip′i•ence *n.* —**in•cip′i•ent•ly** *adv.*
in•ci•pit (in′sĭ-pĭt′, ing′kĭ-) *n.* The be
words of the text of a medieval manusc
book. [Lat., third pers. sing. pr.t. of *in*
INCEPTION.]
in•cise (in-sīz′) *tr.v.* **-cised, -cis•ing, -cis•**
with a sharp instrument: *incised the*
2.a. To engrave (designs, for example) i
b. To engrave designs, writing, or other
ciser < OFr. *enciser* < VLat. **incisāre*; f
incis- : *in-*, in; see IN-² + *caedere*, to c
in•cised (in-sīzd′) *adj.* **1.** Cut into a
2. Made with or as if with a sharp instru
sharply cut: *the incised margin of a leaf*
in•ci•sion (in-sĭzh′ən) *n.* **1.** The act of inc
cut into a body tissue or organ, esp. du
scar resulting from such a cut. **3.** A not
a leaf. **4.** The condition or quality of be
in•ci•sive (in-sī′sĭv) *adj.* Penetrating, cle
expression. —**in•ci′sive•ly** *adv.* —**in•c**
in•ci•sor (in-sī′zər) *n.* A tooth for cutting
at the front of the mouth along the ape
in•cite (in-sīt′) *tr.v.* **-cit•ed, -cit•ing, -ci**
urge on: *inciting workers to strike.* [ME
citer < Lat. *incitāre*, to urge forward : *in*
IN-² + *citāre*, to stimulate, freq. of *ciēre*,
kei-³*.] —**in•cite′ment** *n.* —**in•cit′er** *n.*
in•ci•vil•i•ty (in′sĭ-vĭl′ĭ-tē) *n., pl.* **-ties. 1**
dition of being uncivil. **2.** An uncivil or
incl. *abbr.* **1.** Including. **2.** Inclusive.
in•clasp (in-klăsp′) *v.* Var. of **enclasp.**
in•clem•ent (in-klĕm′ənt) *adj.* **1.** Storm
2. Showing no clemency; unmerciful. —
in•clin•a•ble (in-klī′nə-bəl) *adj.* **1.** Havi
cy or disposition; inclined. **2.** Favorably
in•cli•na•tion (in′klə-nā′shən) *n.* **1.** Th
the state of being inclined; a bend or tilt
the degree of deviation from the horizont
b. An inclined surface; a slope. **3.** A ter
tain condition. **4.** A characteristic dispos
favor one thing rather than another; a
in•cline (in-klīn′) *v.* **-clined, -clin•ing, -**
deviate from the horizontal or vertical;
posed to a certain preference, opinion,
3. To lower or bend the head or body,
—*tr.* **1.** To cause to lean, slant, or slop
have a certain tendency; dispose. **3.** To b
or bow. —*n.* (in′klīn′). An inclined su
dient. [ME *enclinen* < OFr. *encliner* <
into, toward; see IN-² + *-clīnāre*, to le
clin′er *n.*

Syns: incline, bias, dispose, pre
meaning shared by these verbs is "to i
enced toward a particular attitude or c
*clined to believe him; is biased in her fa
admire him; predisposed to studying.* S
in•clined (in-klīnd′) *adj.* **1.** Sloping,
2. Having a preference, disposition, or
inclined plane *n.* A plane set at an angle
to raise or lower a load by rolling or s
in•cli•nom•e•ter (in′klə-nŏm′ĭ-tər) *n.*
to determine the angle of the earth's ma
to the horizontal plane. **2.** An instrun
inclination of an aircraft or a ship rela
3. See **clinometer.**
in•close (in-klōz′) *v.* Var. of **enclose.**
in•clude (in-klo͞od′) *tr.v.* **-clud•ed, -clu**
take in as a part, an element, or a mem
a secondary or subordinate element. **3.**
place into a group, class, or total. [ME
clūdere, to enclose : *in-*, in; see IN-² +
—**in•clud′a•ble, in•clud′i•ble** *adj.*

in•ci•dence (ĭn′sĭ-dəns) *n.* 1. The act or an instance of happening; occurrence. 2. Extent or frequency of occurrence: *a high incidence of malaria*. 3. *Phys.* a. The arrival of radiation or a projectile at a surface. b. Angle of incidence.

EXHIBIT B

THE CONCISE OXFORD DICTIONARY

OF CURRENT ENGLISH

Edited by
H. W. FOWLER AND F. G. FOWLER
based on
The Oxford Dictionary

FIFTH EDITION
Revised by
E. McINTOSH
Etymologies revised by
G. W. S. FRIEDRICHSEN

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PREFACE TO THE FIFTH EDITION

In this edition the etymologies have been thoroughly revised, and for the most part rewritten, by G. W. S. Friedrichsen, to whom I express my sincere thanks for undertaking a laborious task.

Numerous correspondents have sent in useful suggestions for improving the dictionary, all of which are gratefully acknowledged and many of which have been adopted in part or in full. Particular mention must be made of the contributions of P. B. M. Allan, R. W. Burchfield (who read through the proofs), the late Dr R. W. Chapman, L. F. Schooling, and G. C. Vanneck.

With regard to hyphening, some doubt is often felt when the hyphen in a word coincides with the end of a line. To clarify the matter a true hyphen is repeated at the beginning of the following line.

E. McI., 1963

PREFACE TO THE FOURTH EDITION

In this completely revised and reset edition numerous corrections and additions have been made to bring the book up to date. Thanks are due to the many correspondents who have pointed out errors or suggested improvements. Especially must I express my gratitude to Dr Scholes, Dr Honeyman, and Mr J. M. Wyllie for the valuable assistance given for musical terms, chemical terms, and many technical terms. The officials of the Clarendon Press too, past and present, have throughout been most helpful.

In this edition the system of pronunciation devised for the *Pocket Oxford Dictionary* has been adopted, the senses have been usually numbered, the general abbreviations have been collected into an appendix, and the swung dash has been freely employed.

Swung dash (~).

To save space the 'swung dash' or 'tilde' is very frequently used in the body of the article or the list of derivatives. It represents either the complete word at the beginning of the article or the uninflected part of that word often marked by a vertical line. As, for example, in the article **repeat**, ~ stands for *repeat* (*or* repeat), ~*ed* for *repeated*, ~ED[LY][2] for REPEATEDLY[2], ~*ing* for *repeating*, ~ER[1] for REPEATER[1]; and in the article **reverber|ate** we have ~*ating*, ~ate, ~ATORY, ~ATION, ~ATIVE, ~ANT representing *reverberating*, REVERBERATE, REVERBERATORY, REVERBERATION, REVERBERATIVE, REVERBERANT.

E. McI., 1950

in'chŏgate (in-kŏ-), a. Just begun; undeveloped. [f. L IN-[1](*coharc, choare*), see -ATE[2]]

in'chŏ|āte[2] (in-kŏ-), v.t. Begin; originate. So ~A'TION n., ~ĀTIVE (*or* -kŏ'a-) a. [prec., -ATE[3]]

in'cidence, n. Falling on, contact with, a thing; *what is the ~ of the tax?*, on whom will it fall? (Phys.) falling of line, or of thing, moving in a line, upon a surface; *angle of ~*, that which the incident line, ray, etc., makes with the perpendicular to the surface at point of ~; range, scope, extent, of influence. [ME, f. OF (as INCIDENT[2], see -ENCE)]

in'cident[1], n. Subordinate or accessory event; event, occurrence; hostile clash of e.g. troops of countries not at war, as *frontier ~*; detached event attracting general attention; distinct piece of action in play or poem; (Law) privilege, burden; etc., attaching to estate etc. [ME, f. OF (as foll.)]

in'cident[2], a. Apt to occur, naturally attaching, *(to)*; (Law) attaching *to* (cf. prec.); (of light etc.) falling, striking, *(upon)*. [ME, f. OF, or L IN-[1](*cidere* = *cadere* fall), see -ENT]

incidĕn'tal, a. & n. Casual, not essential; liable to happen *to*; *~ images, colours* (perceived as consequence of impressions no longer present); *~ music* (introduced during the action of a play). Hence ~LY[2] adv. (also, loosely, by the way, parenthetically).

incin'er|āte, v.t. Reduce to ashes; consume (body etc.) by fire. Hence or cogn. ~A'TION, ~ātor, nn. [INCINERAT[1]+-AL] [f. med. L IN-[1](*cinerare f. cinis -eris* ashes), see -ATE[3]]

incip'i|ent, a. Beginning; in an initial stage. Hence ~ENCE, ~ENCY, nn., ~ENTLY[2] adv. [f. L as INCEPT, see -ENT]

in'cipit, sent. n. (Here) begins (book etc.), cf. EXPLICIT[1]. [L]

incise' (-z), v.t. Make a cut in; engrave; [f. F *inciser* f. L IN-[1](*cidere cis-* = *caedere* cut)]

inci'sion (-zhn), n. Cutting into a thing; cut, division produced by cutting, notch. [ME, f. OF f. L *incisionem* (prec., -ION)]

incis'ive, a. Cutting, penetrating; (fig.) mentally sharp; acute, trenchant. Hence ~LY[2] (-vl-) adv., ~NESS (-vn-) n. [F (*-if, -ive*), or f. med. L *incisivus* (as INCISE, see -IVE)]

incis'or (-z-), n. Any tooth between the canine teeth in either jaw. [med. L, = cutter (as INCISE, see -OR)]

incite', v.t. Urge, stir up, (person etc. *to* action, *to* do). Hence or cogn. **Incita'tion**, ~MENT (-tm-), nn. [late ME, f. F *inciter* f. L IN-[1](*citare* rouse frequent. of *ciēre cit-*)]

incivil'ity, n. Rudeness; discourtesy. [f. F *incivilité* or LL IN-[1](*civilitas* CIVILITY)]

in'civism, n. Want of good citizenship, esp. of loyalty to French Revolution principles. [f. F IN-[2](*civisme* f. L *civis* citizen)]

‖**In'clearing**, n. The cheques etc. collectively payable by a bank & received through clearing-house for settlement. [IN adv.]

inclĕm'ent, a. (Of weather or climate) severe, esp. cold or stormy. So ~ENCY n. [f. F, or L IN-[2](*clemens* CLEMENT)]

inclin'able, a. Inclined, disposed, *(to* thing, *to* do); favourable *(to)*. [ME, f. OF *enclinable* (as INCLINE[2], see -ABLE)]

inclinā'tion, n. Leaning, slope, slant; difference of direction of two lines, esp. as measured by angle between them; disposition, propensity, *(to, for, towards* thing, *to* do); liking, affection, *(for)*. [ME, f. OF, or f. L *inclinatio* (foll., -ATION)]

incline'[1], v.t. & i. Bend (head, body, one*self*) forward or downward; *~ one's ear*, listen favourably *(to* person, prayer, etc.); dispose (mind, heart, person, *to* do), *as ~ our hearts to keep this law, I am ~d to think*; be disposed, as *I ~ to think*; lean, cause to lean, from the vertical etc.; *~d* (sloping) *plane*, one of the MECHANICAL *powers*; tend *(to* corpulence etc.). [ME *en-* f. OF *encliner* f. L IN-[1](*clinare* bend)]

in'cline[2] (*or* -in'), n. Inclined plane; slope. [f. prec.]

inclinŏm'eter, n. Instrument measuring vertical intensity of earth's magnetic force as shown by dip of magnetic needle, or for measuring slope. [INCLINE+-METER]

includ|e' (-lōō-), v.t. Comprise, embrace, (thing etc.) as part of a whole; (part in abs. constr.) if we *~e*, *as seven were killed, ~ing the guard*; treat, regard, as so comprised; *~e out*, (specifically) exclude; (p.p.) shut in. [ME, f. L IN-[1](*cludere clus-* = *claudere* shut)]

inclus'ive (-lōō-), a. Including; comprising, (*of*, or abs.); (abbr. *incl.*) *pages 7 to 28 ~* (including pages 7 & 28); including much or all, as *~ terms* (at hotel etc.). Hence or cogn. **inclu'sion** (-lōōzhn) n. ~LY[2] adv., ~NESS n. [f. med. L *inclusivus* (as prec., see -IVE)]

incŏg', n., & adv. Colloq. abbr. of foll.

incŏg'nĭto, a. & n. (pl. *-ti* pron. -tē; fem. *-ta* pron. -ta, pl. *-te* pron. -tā), & adv. (Person) concealed under disguised character; (adv.) with one's name, character, etc., concealed, as *travel, go good, ~*. [It., = unknown, f. L IN-[3](*cognitus* p.p. of *cognoscere* get to know)]

incŏgn'izable (-kŏgn-, -kŏn-), a. That cannot be apprehended by senses or intellect. [IN-[3]]

incŏgn'iz|ant (as prec.), a. Unaware, unconscious *of*. So ~ANCE n. [IN-[3]]

incŏhĕr'|ent, a. Not coherent (lit. & fig.). So ~ENCE n., ~ENTLY[2] adv. [IN-[3]]

incŏhĕs'ive, a. Not cohesive. [IN-[3]]

incombŭs'tible, a. That cannot be consumed by fire. Hence ~IBIL'ITY n. [f. med. L IN-[3](*combustibilis* COMBUSTIBLE)]

in'come, n. Periodical (usu. annual) receipts from one's business, lands, work, investments, etc.; *~-tax* (levied on this). [IN adv.]

in'com'er (-kŭ-), n. One who comes in; immigrant; intruder; successor. [IN adv.]

in'com'ing[1] (-kŭ-), n. Entrance, arrival; (usu. pl.) revenue, income. [IN adv.]

in'coming[2] (-kŭ-), a. Succeeding; immigrant; (of profit) accruing. [IN adv.]

incommĕn'surable (-sher-), a. (Of magnitudes) having no common measure integral or fractional (*with* another); irrational, surd; not comparable in respect of magnitude; not worthy to be measured *with*. Hence ~ABIL'ITY n., ~ABLY[2] adv. [f. LL IN-[3](*commensurabilis* COMMENSURABLE)]

incommĕn'surate (-sher-), a. Out of proportion, inadequate, (*with, to*); = prec. Hence ~NESS n. [IN-[3]]

incommōde', v.t. Trouble, annoy; hinder. [f. F *incommoder* or L IN-[2](*commodare* f. *commodus* COMMODIOUS)]

incommōd'ious, a. Not affording good accommodation, uncomfortable. Hence ~NESS n. [IN-[3]]

incommūn'ic|able, a. That cannot be shared; that cannot be told. Hence ~ABIL'ITY, ~ableness, nn., ~ably[2] adv. [f. F, or LL IN-[3](*communicabilis* COMMUNICABLE)]

incommūnica'dō (-ah-), a. Without means of communication, (of prisoner) in solitary confinement. [Sp. (*-omu-*)]

incommūn'icative, a. Not communicative. Hence ~LY[2] adv., ~NESS n. [IN-[3]]

incommūt'able, a. Unchangeable; not commutable. Hence ~LY[2] adv. [ME, f. OF, or L IN-[3](*commutabilis* COMMUTABLE)]

incompăct', a. Not compact (esp. fig.). [IN-[3]]

incŏm'parable, a. Matchless; not to be compared (*with, to*). Hence ~leness n., ~LY[2] adv. [ME, f. OF f. L IN-[3](*comparabilis* COMPARABLE)]

incompăt'ible, a. Opposed in character, discordant; inconsistent (*with*). So ~IBIL'ITY n. [f. OF, or med. L IN-[3](*compatibilis* COMPATIBLE)]

incŏm'pĕt|ent, a. Not qualified or able (*to* do); not legally qualified. Hence or cogn. ~ENCE, ~ENCY, nn., ~entLY[2] adv. [f. F, or LL IN-[3](*competens* COMPETENT)]

incomplēte', a. Not complete. Hence ~LY[2] (-tl-) adv., ~NESS (-tn-) n. [ME, f. OF, or LL IN-[3](*completus* COMPLETE)]

incomprĕhĕn'sible, a. That cannot be understood; (Athanas. Creed) boundless (also as n., *three ~ibles*). Hence ~IBIL'ITY, ~ibleness, nn., ~IBLY[2] adv. [ME, f. L IN-[3](*comprehensibilis* COMPREHENSIBLE)]

incomprĕhĕn'sion (-shn), n. Failure to understand. [IN-[3]]

incompress'ible, a. That cannot be compressed. Hence ~IBIL'ITY n. [IN-[3]]

incomput'able, a. That cannot be computed. [IN-[3]]

inconceiv'able (-sēv-), a. That cannot be imagined; (pop.) very remarkable. Hence ~ABIL'ITY n., ~ably[2] adv. [IN-[3]]

inconclus'ive (-klōō-), a. (Of argument, evidence, action) not decisive or convincing. Hence ~LY[2] adv., ~NESS n. [IN-[3]]

incondĕn'sable, a. That cannot be condensed, esp. that cannot be reduced to liquid or solid condition. [IN-[3]]

incŏn'dite, a. (Of literary composition etc.) ill constructed; crude, unpolished. [f. L IN-[3](*conditus* p.p. of *condere* put together)]

inconfŏrm'ity, n. Dissimilarity, want of conformity, *(to, with)*; = NONCONFORMITY. [IN-[3]]

incŏng'ruous (-kŏnggrōō-), a. Disagreeing, out of keeping, *(with)*; out of place, absurd. Hence or cogn. **Incongru'ity** (-grōō-), ~NESS, nn., ~LY[2] adv. [f. L IN-[3](*congruus* CONGRUOUS)]

inconsĕc'utive, a. Wanting in sequence, inconsequent. Hence ~LY[2] adv., ~NESS n. [IN-[3]]

incŏn'sequ|ent, a. Not following naturally, irrelevant; wanting in logical sequence; disconnected. Hence or cogn. ~ENCE n., ~ĕn'tial (-shal) a., ~ĕn'tially[2] (-shal-), ~entLY[2], advv. [f. L IN-[3](*consequens* CONSEQUENT)]

inconsid'erable, a. Not worth considering; of small size, value, etc. [f. F, or IN-[3]+CONSIDERABLE]

inconsid'er|ate, a. (Of person or action) thoughtless, rash; lacking in regard for feelings etc. of others. Hence or cogn. ~ately[2] adv., ~ateness, ~A'TION, nn. [f. L IN-[3](*consideratus* CONSIDERATE)]

inconsis't|ent, a. Not in keeping, discordant, incompatible, *(with)*; (of single thing) having ~ent parts; acting at variance with one's own principles or former conduct. Hence ~ENCY n., ~entLY[2] adv. [IN-[3]]

inconsōl'able, a. (Of person, his grief, etc.) that cannot be consoled. Hence ~LY[2] adv. [f. F, or L IN-[3](*consolabilis* CONSOLABLE)]

incŏn'son|ant, a. Not harmonizing *(with, to)*. Hence ~ANCE n. [IN-[3]]

inconspic'uous, a. Not conspicuous; (Bot., of flowers) small, pale, or green. Hence ~NESS n. [f. LL IN-[3](*conspicuus* CONSPICUOUS)]

incŏn'st|ant, a. (Of person) fickle, changeable; variable, irregular. Hence or cogn. ~ANCY n., ~antLY[2] adv. [ME, f. OF f. L IN-[3](*constantem* CONSTANT)]

inconsūm'able, a. That cannot be consumed by fire etc.; (Pol. Econ.) not meant to be consumed in use. [IN-[3]]

incontĕs'tab|le, a. That cannot be disputed. Hence ~LY[2] adv. [F (IN-[3])]

In wds from *in-clearing* to *incurve*, pronounce in-k-, not ingk-.

in'cidence, n. Falling on, contact with, a thing; *what is the ~ of the tax?*, on whom will it fall?; (Phys.) falling of line, or of thing, moving in a line, upon a surface; *angle of ~*, that which the incident line, ray, etc., makes with the perpendicular to the surface at point of ~; range, scope, extent, of influence. [ME, f. OF (as INCIDENT[2], see -ENCE)]

EXHIBIT C

REDACTED

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on June 4, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filings(s) to the following:

Mary B. Matterer
MORRIS, JAMES, HITCHENS & WILLIAMS, LLP

I also certify that copies were caused to be served on June 4, 2007, upon the following in the manner indicated:

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